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A STUDY OF THE REARRANGEMENT PRODUCTS  
FROM ISOXAZOLOPYRIDINIUM SALTS.

by

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University of Keele in  
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of Doctor of Philosophy

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University of Keele

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### Abstract

Brief treatment of tetrahydro-4-oxoisoxazolo [2,3-a] pyridinium bromide and its 3-methyl derivative with boiling acetic anhydride gave 4-acetyl-5,6-dihydro-4H-furo [3,2-b] pyrid-2-one and its 3-methyl counterpart. The structures of these rearrangement products have been proved by complete hydrogenation, spectroscopy and X-ray diffraction studies. The 2-methylisoxazolo [2,3-a] pyridinium salt did not undergo the rearrangement; this suggests a keten or an isoxazoline intermediate.

When 4,5,6,7-tetrahydro-4-hydroximinisoxazolo [2,3-a] pyridinium bromide or chloride were heated with acetic anhydride, rearrangement to 4-acetyl-7-halogeno-5,6-dihydro-4H-pyrrolo [3,2-b] pyrid-2-one occurred. Mechanisms for the rearrangement have been suggested.

Photolysis of the rearrangement products led to the isolation of dimers. Photolysis of 5,6-dihydro-4H-furo [3,2-b] pyrid-2-one gave a dimer when using benzene as the solvent; when methanol was used 4-hydroxy-3-methoxymethylamino-hexa-2,4-dienoic acid lactone was produced.

## Contents.

### PART I.

	<u>Page.</u>
<u>Introduction.</u>	
Nomenclature	1.
Synthesis of isoxazolium salts.	2.
Reactions of isoxazolium salts with nucleophiles.	
1. 3-unsubstituted isoxazolium salts.	3.
2. 5-unsubstituted isoxazolium salts.	18.
3. 2,3,5-trisubstituted isoxazolium salts.	33.
Uses in peptide synthesis.	37.
Uses in photography.	47.
<u>Discussion.</u>	
(i) Introduction.	48.
(ii) Furopyridones.	50.
(iii) Mechanisms for the rearrangement.	78.
(iv) 3-(4-bromobutyryl) isoxazole.	97.
(v) Pyrrolopyridones.	104.
<u>Experimental.</u> Preliminary notes.	113.
<u>References.</u>	141.

### PART II.

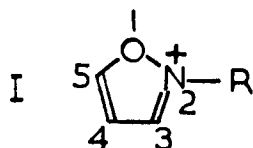
<u>Introduction.</u>	147.
<u>Discussion.</u>	156.
<u>Experimental.</u>	171.
<u>References.</u>	177.

## PART I

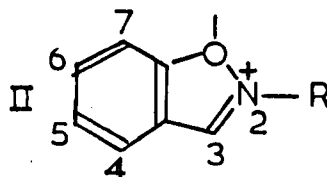
# INTRODUCTION

## Nomenclature

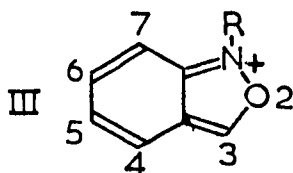
Throughout the course of this work the monocyclic salts will be numbered and named as shown by I. The bicyclic systems will be numbered and named according to the rules set down by the American Chemical Society Ring Index except for compounds of type III which may be referred to for convenience as anthranilium salts.



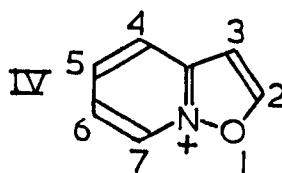
Isoxazolium Salts



1,2-Benzisoxazolium Salts



2,1-Benzisoxazolium  
Salts



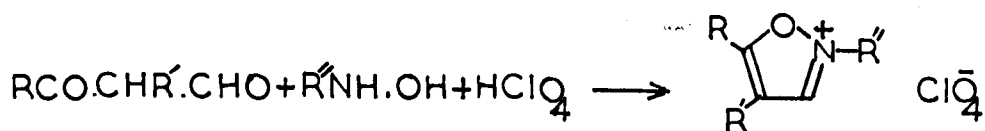
Isoxazolo[2,3-a]  
Pyridinium Salts

# Preparation of Isoxazolium Salts.

These salts are generally prepared by quaternization of the requisite isoxazole by various reagents. Some of the more widely used reagents are; alkyl p-toluenesulphonates<sup>1</sup>, dialkyl sulphates<sup>1,2,3</sup> and trialkyl oxonium fluoroborates.<sup>3,4</sup> Where a branched quaternizing group is required then these can be more efficiently prepared by treating the isoxazole with an appropriate alcohol (which must be a good carbonium ion source) and perchloric acid.<sup>5,6</sup>

In some cases the alkylation may be improved by using sulpholane<sup>2</sup> as a solvent which tends to reduce reaction times, by-product formation and minimizes the purification problems.

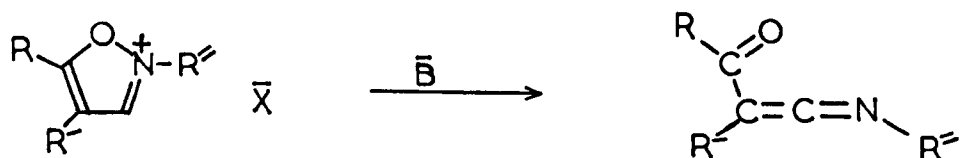
It has been reported<sup>6,7</sup> that in some cases the salts have been satisfactorily prepared by attaching the substituent to nitrogen prior to cyclization. e.g.



## Reactions of Isoxazolium Salts With Nucleophiles.

### 1. 3-unsubstituted isoxazolium salts.

Because 3-unsubstituted isoxazoles undergo ring opening reactions with bases to give  $\beta$ -ketonitriles it was believed<sup>8</sup> that similar isoxazolium salts should be readily converted into the unknown  $\alpha$ -ketoketenimines.



This idea was supported by the discovery of the facile reaction of N-methyl-5-phenylisoxazolium methosulphate with aqueous sodium acetate solution.<sup>8</sup> Such reactions with carboxylic acids and carboxylate anions are dealt with later under "uses in peptide synthesis".

Over a thirty five year period Claisen, Mumm and co-workers reported a number of reactions with various nucleophiles many of which have since been verified.<sup>8</sup>

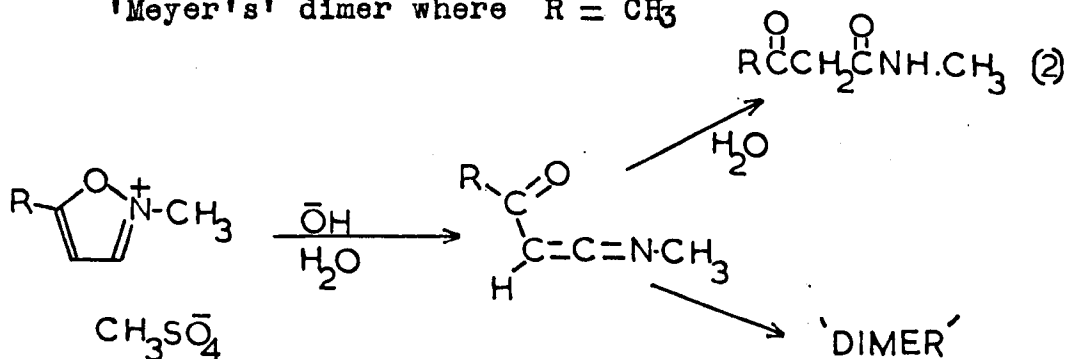
#### (1) Reaction with hydroxide.<sup>8</sup>

Two major products were isolated, the expected acyl acetamide (2), due to addition of water to the ketenimine, and a compound of unknown structure whose analysis and molecular weight correspond to a dimer of the ketoketenimine. Two examples of this dimer are described

in the earlier literature.

'Mumm's' dimer where  $R = C_6H_5$

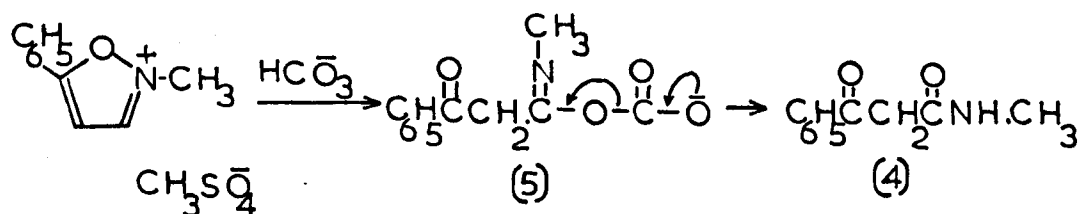
'Meyer's' dimer where  $R = CH_3$



The best structure so far postulated for these 'dimers' is that of the pyridone (3) and a possible mechanism for its production is shown in scheme 1.

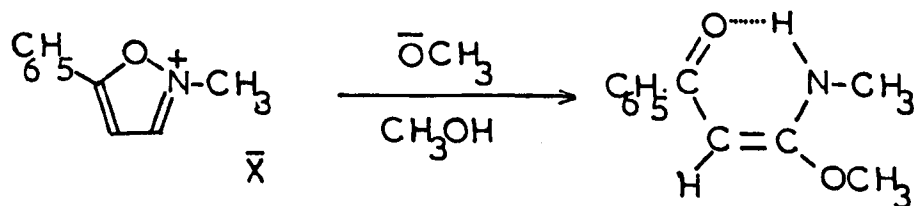
#### (ii) Reaction with bicarbonate.<sup>8</sup>

In this case the acyl acetamide (4) is isolated in almost quantitative yield. It is possible that compound (5) is an intermediate.

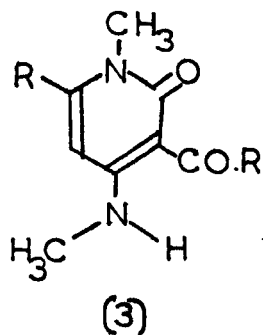
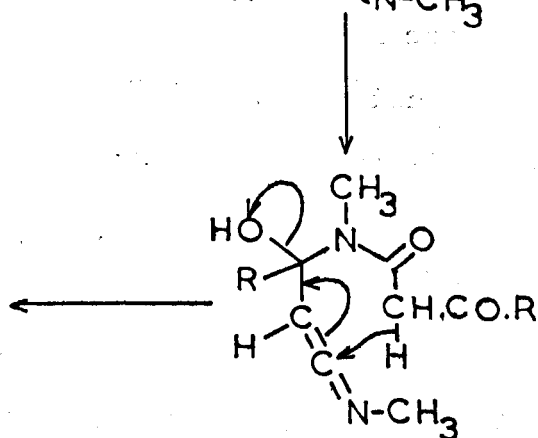
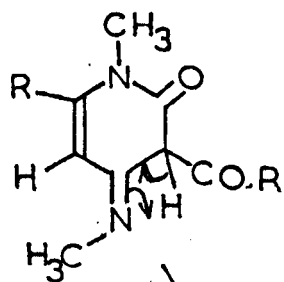
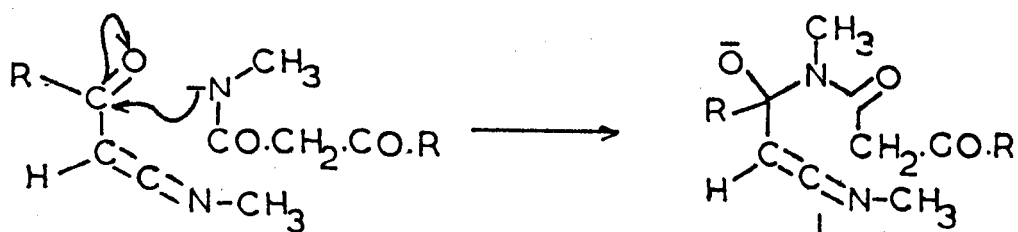
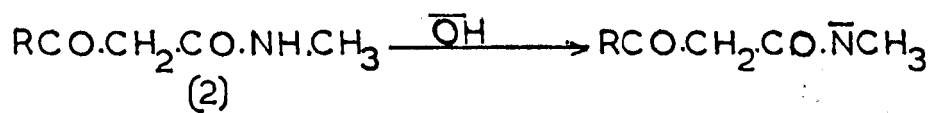


#### (iii) Reaction with alkoxide.

Here the simple addition product of the alcohol and the ketenimine is produced.



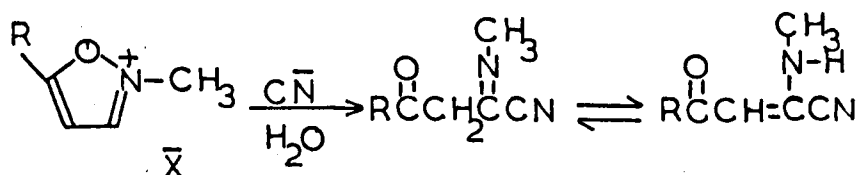
# Scheme 1





(iv) Reaction with cyanide.

Again the simple addition product is isolated but it may exist in its imino or amino forms.



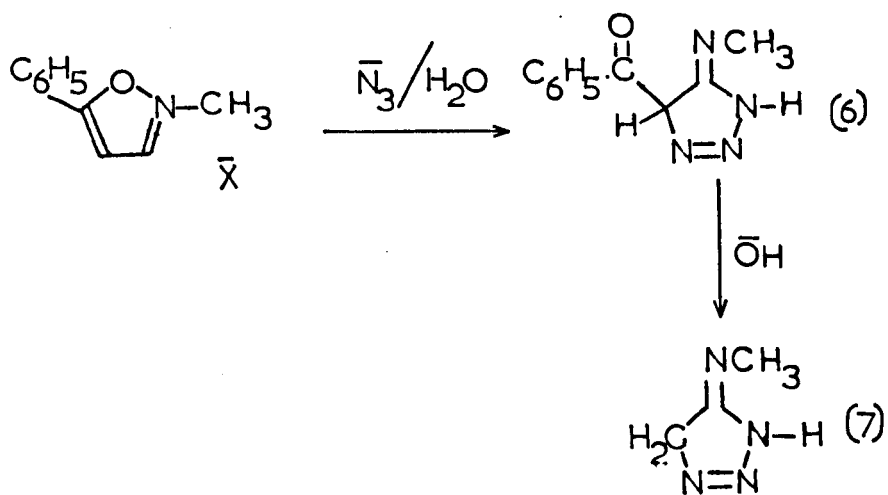
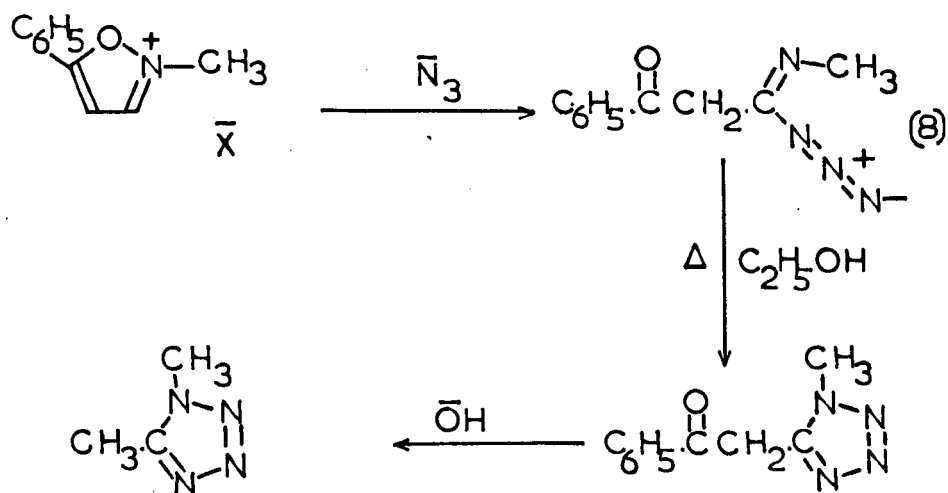
(v) Reaction with azide.<sup>8</sup>

If the isoxazolium salt is dissolved in an aqueous solution of sodium azide and allowed to stand for twentyfour hours the two major products (6) and (7) can be isolated. An additional unstable compound can be isolated by filtering off the precipitate obtained thirty minutes after mixing. This intermediate has an infrared absorption at  $4.69\mu$  which is characteristic of the cumulative double bond azide system and another at  $5.90\mu$  characteristic of a simple acetophenone carbonyl group. This along with an acetophenone type of ultraviolet spectrum suggested the simple imino azide (8). On heating this imino azide in ethanol and subsequent hydrolysis, 1,5-dimethyltetrazole can be isolated. These reactions are shown in scheme 2.

(vi) Reaction with anthranilate.

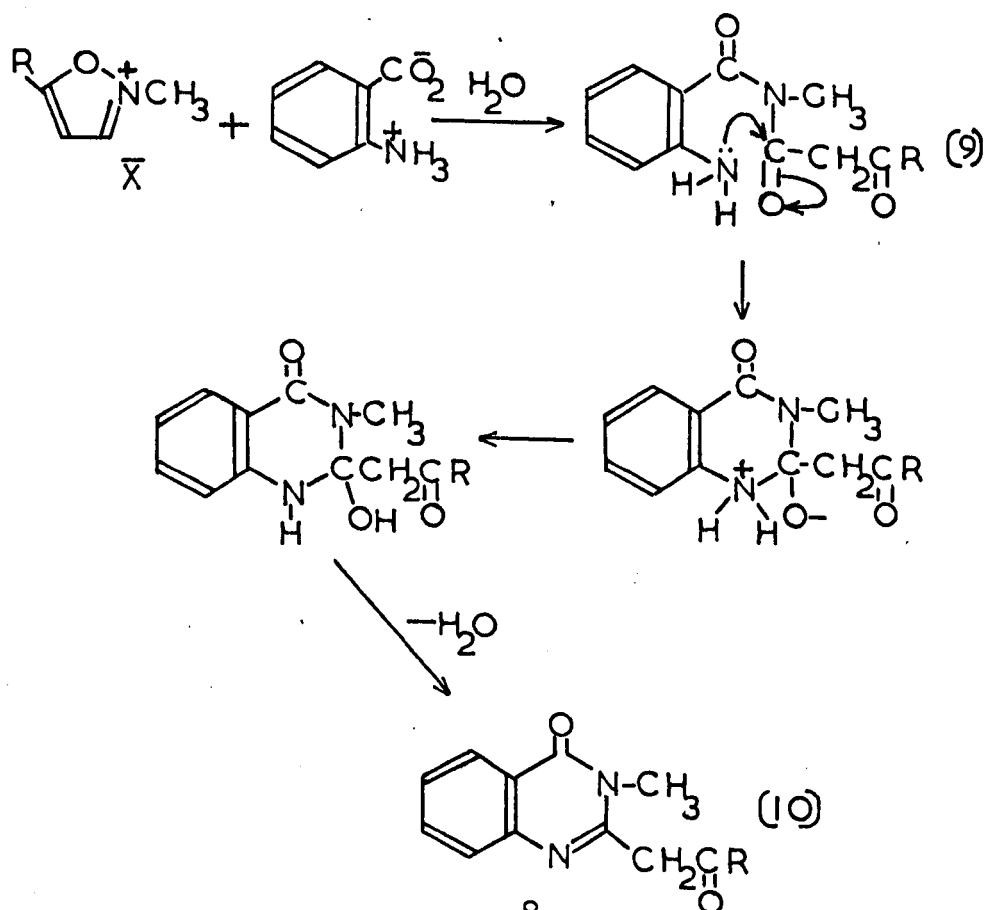
Before considering carboxylate ions with which special rearrangements take place it is worth noting that many yield simple enol ester structures as described

## Scheme 2



under the heading of 'uses in peptide synthesis' e.g. acetic, formic, benzoic, p-toluic, m- and p-nitrobenzoic, chloroacetic, phenylacetic, crotonic and cinnamic acids.

Mumm and Bargell have separately reported that anthranilate yields the quinazalone (10) on reaction with an isoxazolium salt. This can be postulated to occur via the intermediate imide (9).



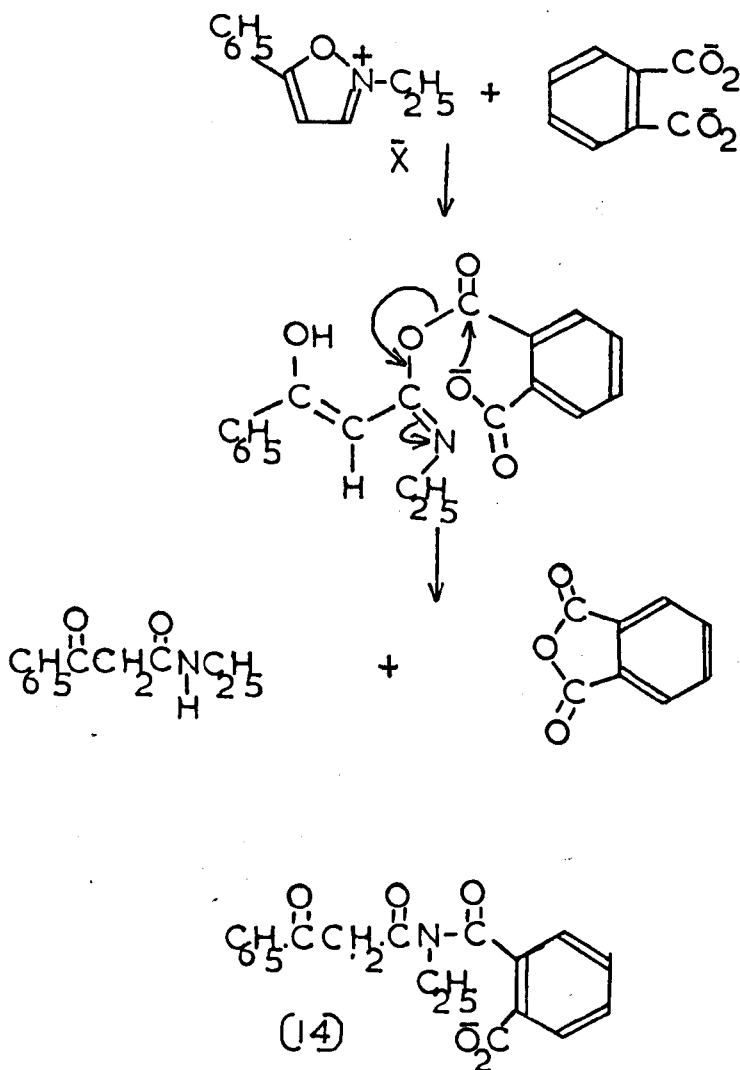
(vii) Reaction with oxalate.<sup>8</sup>

The initial product was the salt (11) which on acidification gave the imide (12); this then on boiling

in water yielded trimethyl paramide (13). A possible mechanism for the production of salt (11) is shown in scheme 3.

(viii) Anhydride formation.<sup>8</sup>

If the dianion of phthalic acid is treated with an isoxazolium salt in acetonitrile, phthalic anhydride is produced, the yield is however disappointing since the rearrangement to the imide (14) also occurs.

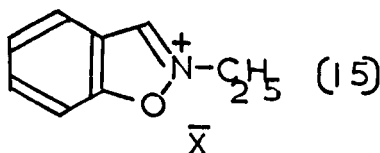




(ix) Other reactions.

These have not been repeated but the structures postulated by Mumm are in accord with the mechanistic interpretation of Woodward and Olofson. They are summarized in scheme 4.

The above examples deal with monocyclic 3-unsubstituted isoxazolium salts; similar ring opening reactions occur with bicyclic systems. The 1,2-benzisoxazolium ion (15) is a 3-unsubstituted isoxazolium salt and may react with nucleophiles in a similar manner.

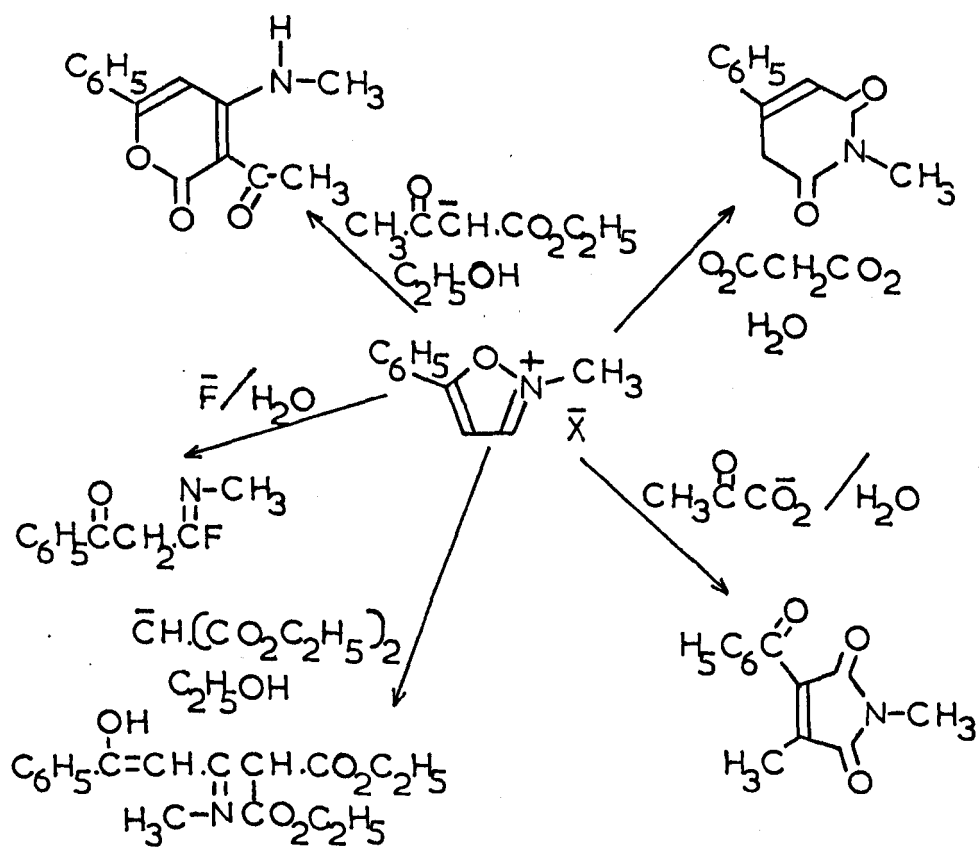


The first benzisoxazole was prepared by Victor Meyer in 1892; however the first N-alkylated salts were not reported until 1931 by Kohler and these contained 3-aryl substituents.

The quaternization of benzisoxazole is not possible with normal alkylating agents since it is too weakly nucleophilic and too heat sensitive. Meerwein's reagent,  $(\text{C}_2\text{H}_5)_3\overset{+}{\text{O}}\cdot\text{BF}_4^-$ , gives the quaternary salt at room temperature in a quantitative yield.<sup>9</sup> These salts are stable in acid but very unstable in neutral or basic media.

In an aqueous solution but in the absence of reactive

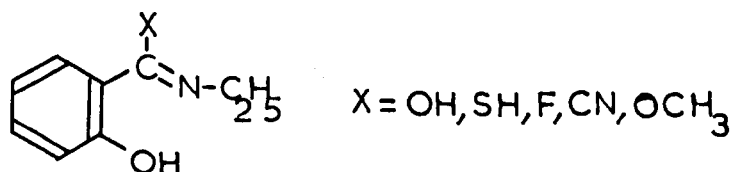
# Scheme 4



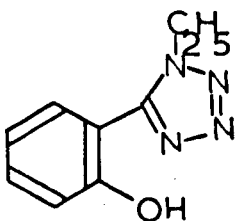
anions N-ethylsalicylamide is the final product. At pH. greater than 7 a yellow polymeric material becomes an important by-product; a similar by-product is obtained when the salt is treated with triethylamine in an organic solvent.<sup>12</sup> Efforts to detect a ketenimine have failed although the products would indicate such an intermediate.

(x) Products from simple nucleophiles.<sup>9</sup>

Hydroxide, hydrosulphide, fluoride, cyanide anions in aqueous solutions or methoxide anions in methanol give high yields of simple products with the following structure:-

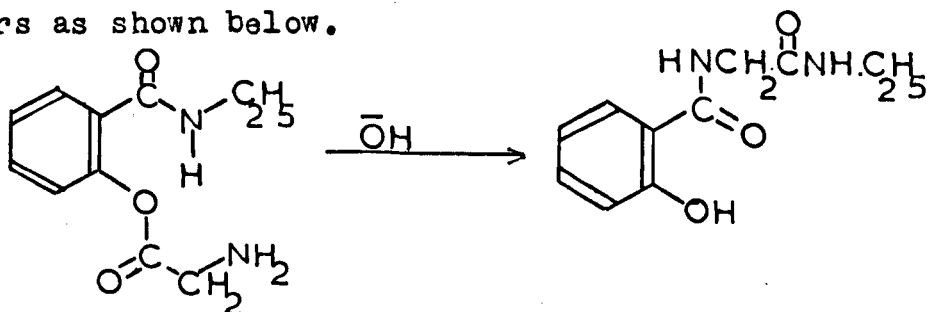


With an azide solution the following tetrazole is obtained:-



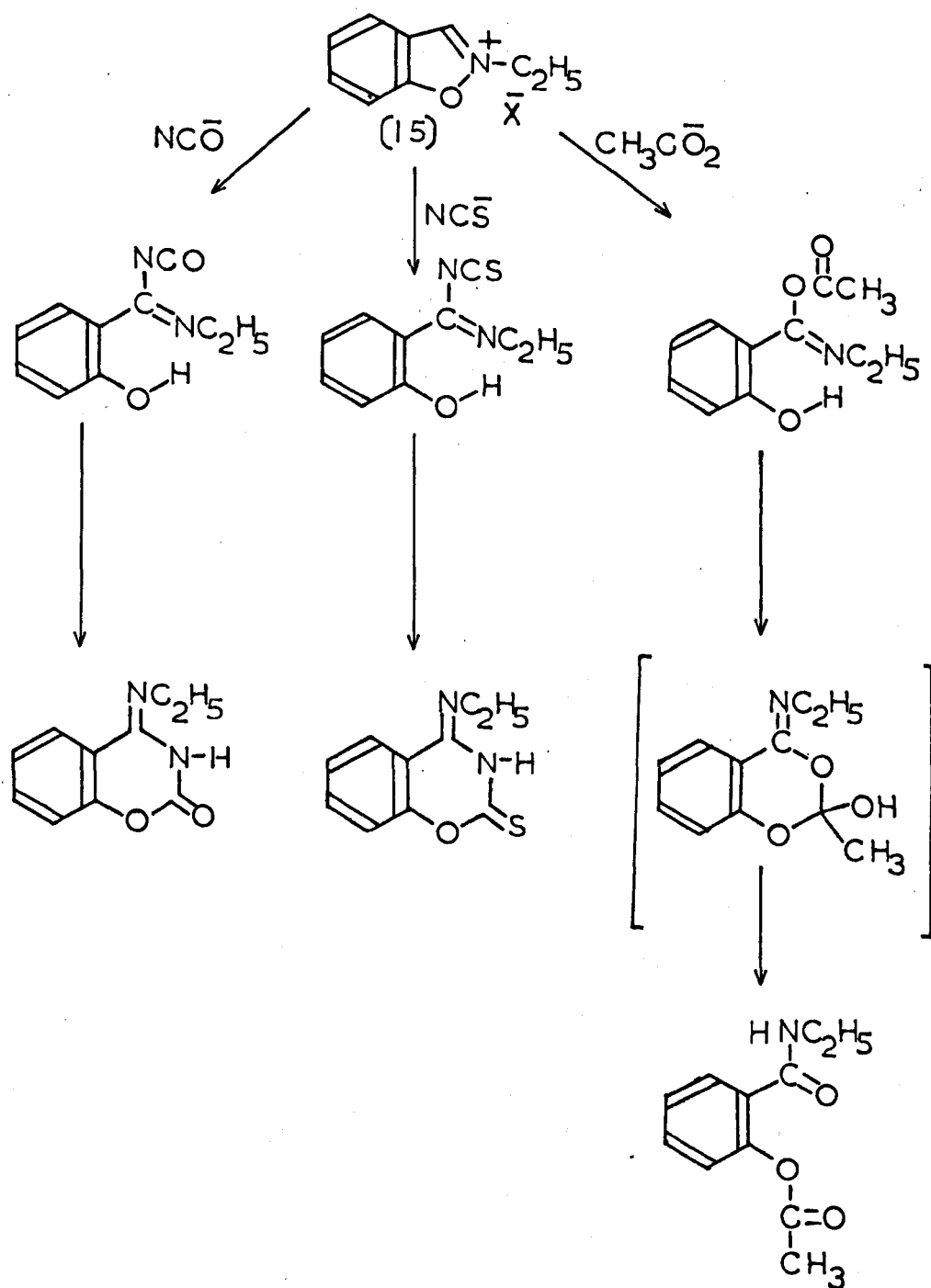
(xi) Products from cyanate, thiocyanate and carboxylate anions.<sup>9</sup>

These reactions are summarized in scheme 5. The acetate anion may be exchanged for benzoate, methoxyacetate or glycine. With glycine, however a further rearrangement occurs as shown below.





# Scheme 5



Production of O-acyl-N-ethylsalicylamides may best be rationalized as proceeding from an imino anhydride, shown in scheme 5.

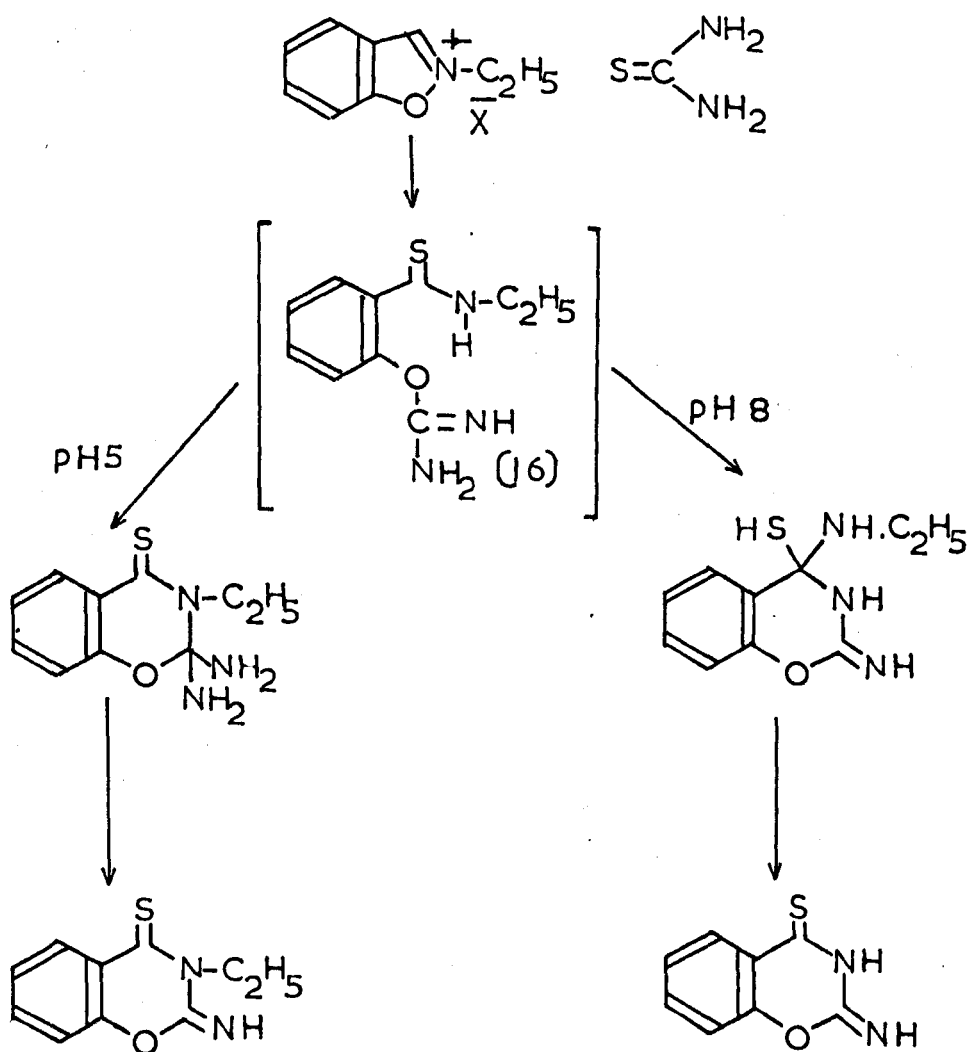
(xii) Reactions with thiourea.<sup>9</sup>

This nucleophile reacts with benzisoxazolium salts to give a yellow solution which then reacts in one of two ways according to the pH. of the medium. The yellow solution probably arises because of the presence of intermediate (16) (See scheme 6).

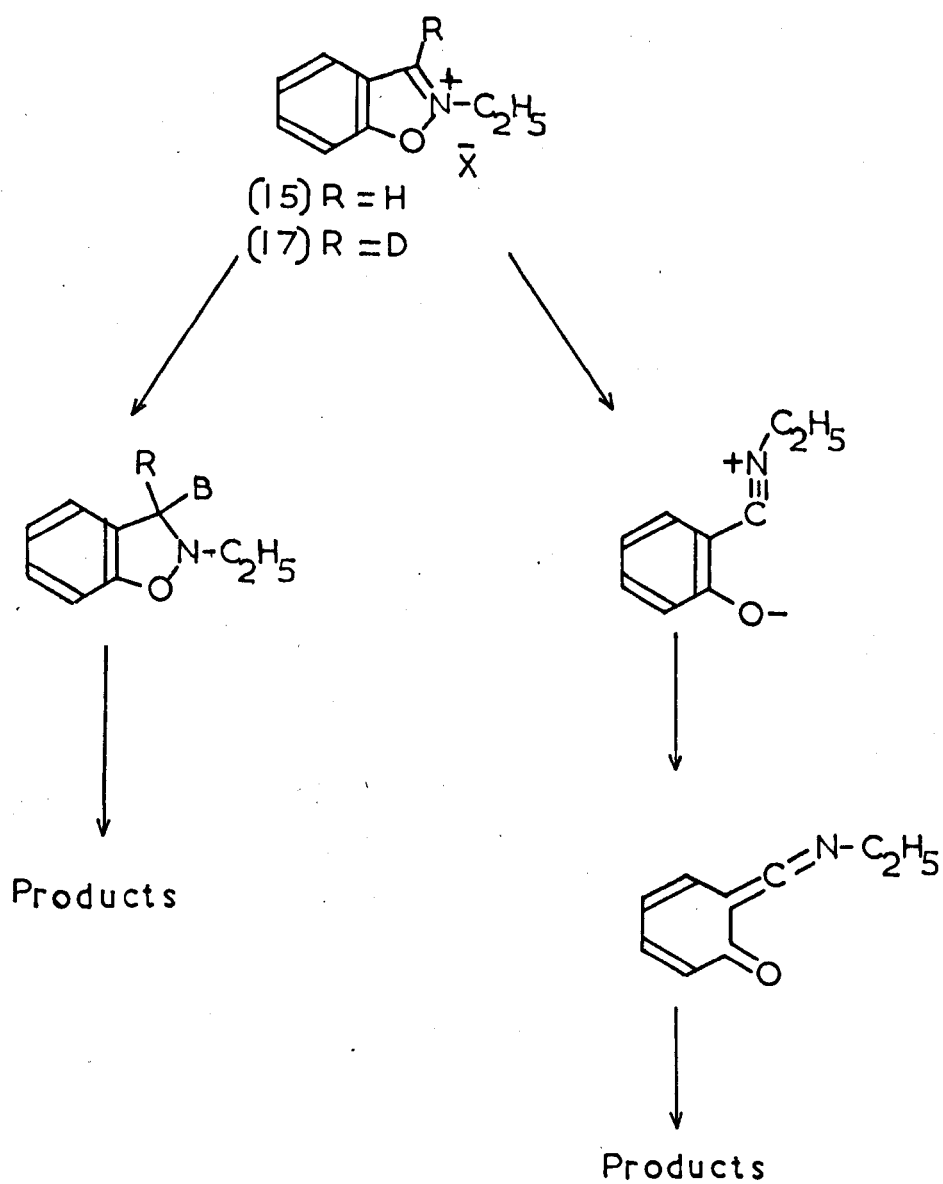
The mechanism of the reaction of benzisoxazolium salts with nucleophiles has not been as completely resolved as it has for the simple isoxazolium salts because in many cases the intermediates are not observable.

Two possible modes of attack are conceivable and these are shown in scheme 7. To try and decide which pathway was operating, reactions of (15) with aqueous acetic acid were carried out.<sup>10</sup> The primary kinetic isotope effect when C<sub>3</sub> has hydrogen, compound (15); or deuterium, salt (17); attached to it requires that the rate determining step involves proton abstraction. It must also be noted that the C-H bond cleavage is irreversible since allowing the salt (17) to decompose in an aqueous bisulphite solution until 60% decomposition had occurred led to isolation of the deuterated salt (17).

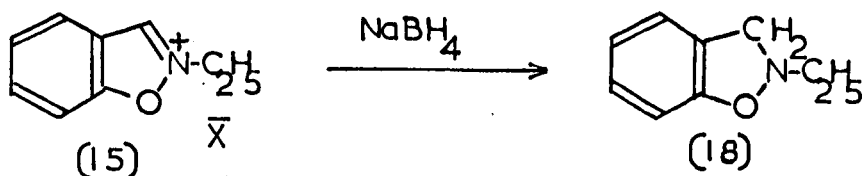
# Scheme 6



# Scheme 7



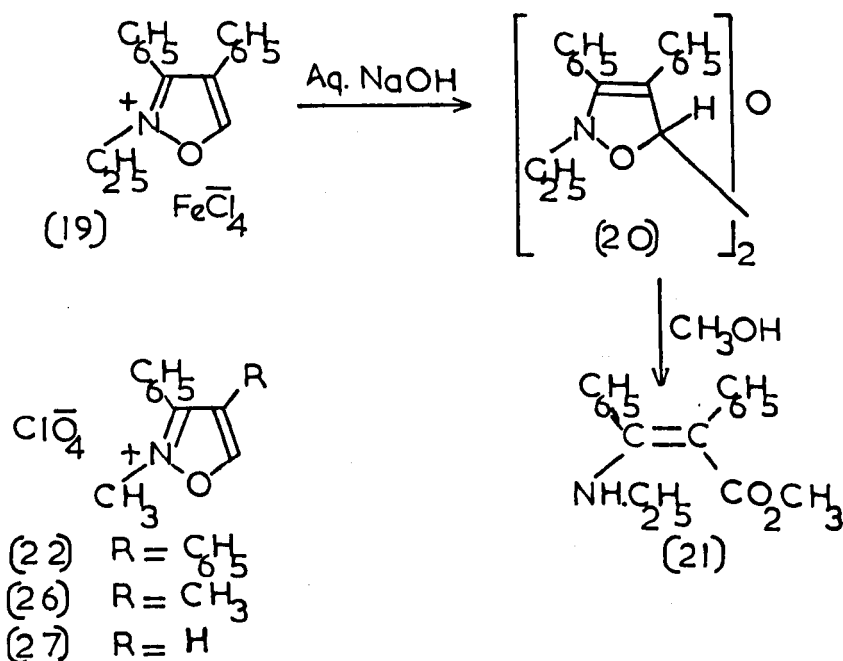
Benzisoxazolines can in fact be excluded as relevant intermediates by studying those obtained by reducing the salt (15) with sodiumborohydride i.e. compound (18).



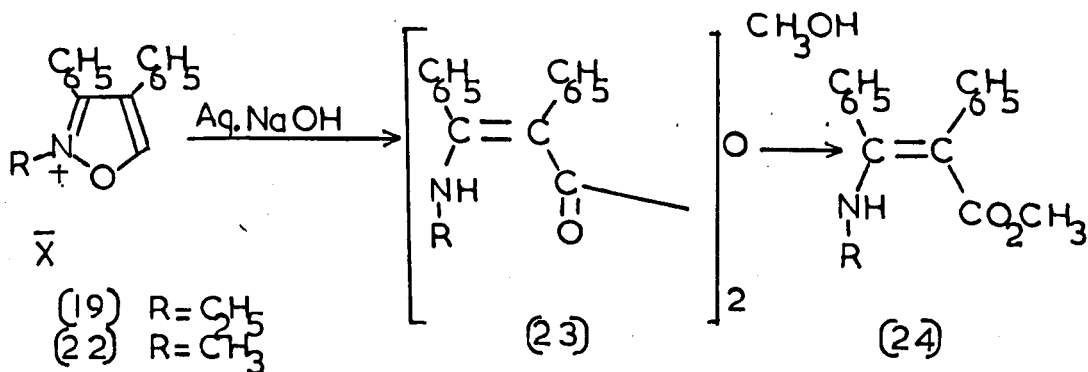
This isoxazoline (18) is stable to acids and bases, it can be recovered in an 80% yield from an aqueous methanolic solution of sodium hydroxide after four days. From this it is clear that the isoxazolines are too stable to act as intermediates in the ring cleavage reactions and the ketoketenimine route is the more highly favoured pathway.

## 2. 5-unsubstituted isoxazolium salts.

(1) Prior to 1969 only one reference has been made to nucleophilic attack on quaternary isoxazolium salts of the 5-unsubstituted series. This work was done by Kohler et al<sup>11</sup> who describe the reaction of 3,4-diphenyl-2-ethyl isoxazolium chloroferrate (19) with sodium hydroxide. The product postulated was the bismolecular anhydride (20) which on methanolysis yielded  $\beta$ -ethyl amino cinnamate (21). The structure of (20) was not proved and in 1969 Adachi and Kano<sup>12</sup> reinvestigated the reactions of the 2,3,4-trisubstituted salts.



By using a similar procedure as Kohler, or by treating the salts with triethylamine in a mixture of water and acetonitrile, products whose molecular formulae were in accord with the anhydride (20) and analogs were obtained.<sup>12</sup> However, since infrared and nuclear magnetic resonance studies show the presence of amino groups the postulated structure can not be correct. The data is more in accord with the cinnamic anhydride derivatives of type (23) which will also give  $\beta$ -alkyl amino cinnamates (24) on methanolysis.



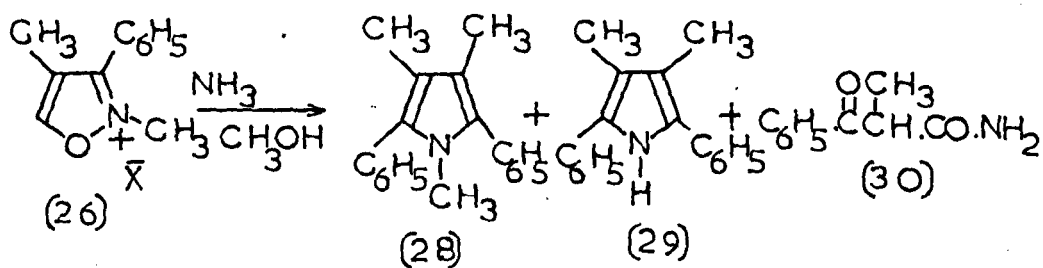
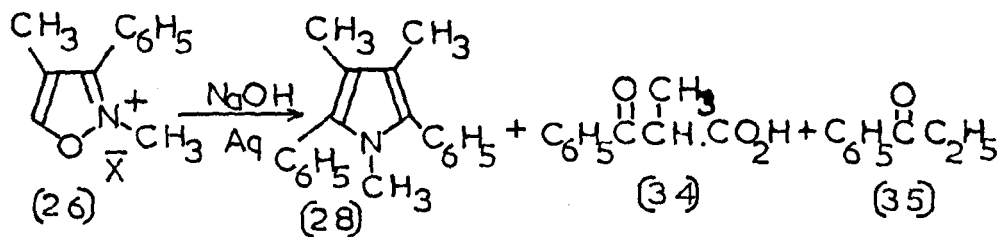
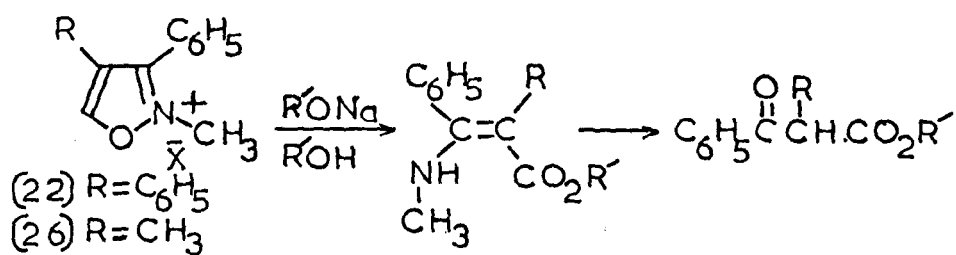
Treatment of salts (22) and (26) with sodium alcoholate gave the corresponding methyl amino cinnamates which could be quantitatively hydrolysed by alcoholic sodium hydroxide to the known  $\beta$ -ketoesters.<sup>12</sup>

On treating the salt (26) with cold aqueous caustic solution an unexpected product (28) was obtained in 30% yield, besides the usual ring cleavage products. If the salt (26) is treated with methanolic ammonia the pyrrole (28) is again produced along with pyrrole (29) (15% and 17% respectively) and the acid amide (30) (See scheme 8). The structures of the pyrroles (28) and (29) were proved by synthesis from 2,3-dibenzoylbutane and ammonia or methylamine.<sup>12</sup>

Reactions of salts (22) and (26) with several primary and secondary amines gave the corresponding acid amides (31) and ketones (32). From salt (26) the pyrrole (28) was also obtained<sup>12</sup> as shown in scheme 9. The  $\beta$ -keto acid amides (31) arose from hydrolysis of their  $\beta$ -methyl amino derivative (33) on passage down an alumina column. None of the pyrrole derivative was detected in any nucleophilic reactions with salts (22) and (27) which suggests that the methyl group at C<sub>4</sub> plays an important role in its formation.

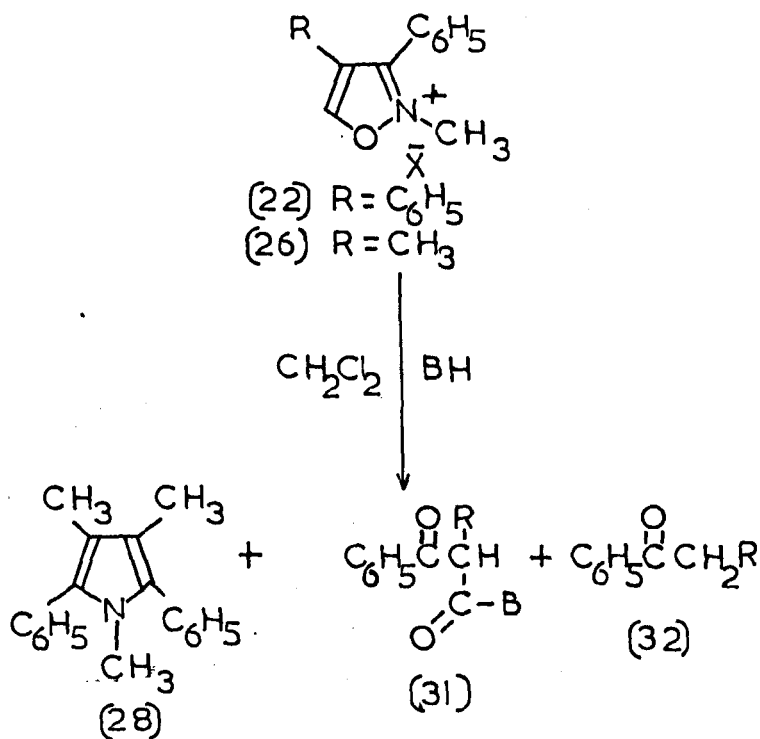
Formation of products (24), (34) and (35) may arise from addition of the nucleophile at C<sub>5</sub> or C<sub>5</sub> proton abstraction and the two abnormal products (28) and (29)

# Scheme 8

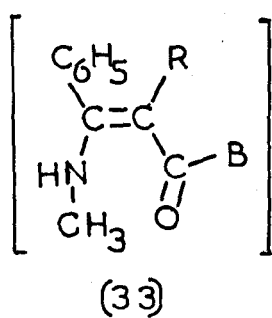




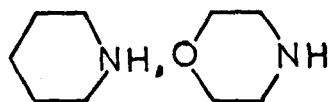
# Scheme 9



Only From Salt (26)



B = CH<sub>3</sub>NH, nC<sub>3</sub>H<sub>7</sub>NH, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>CH<sub>2</sub>NH,



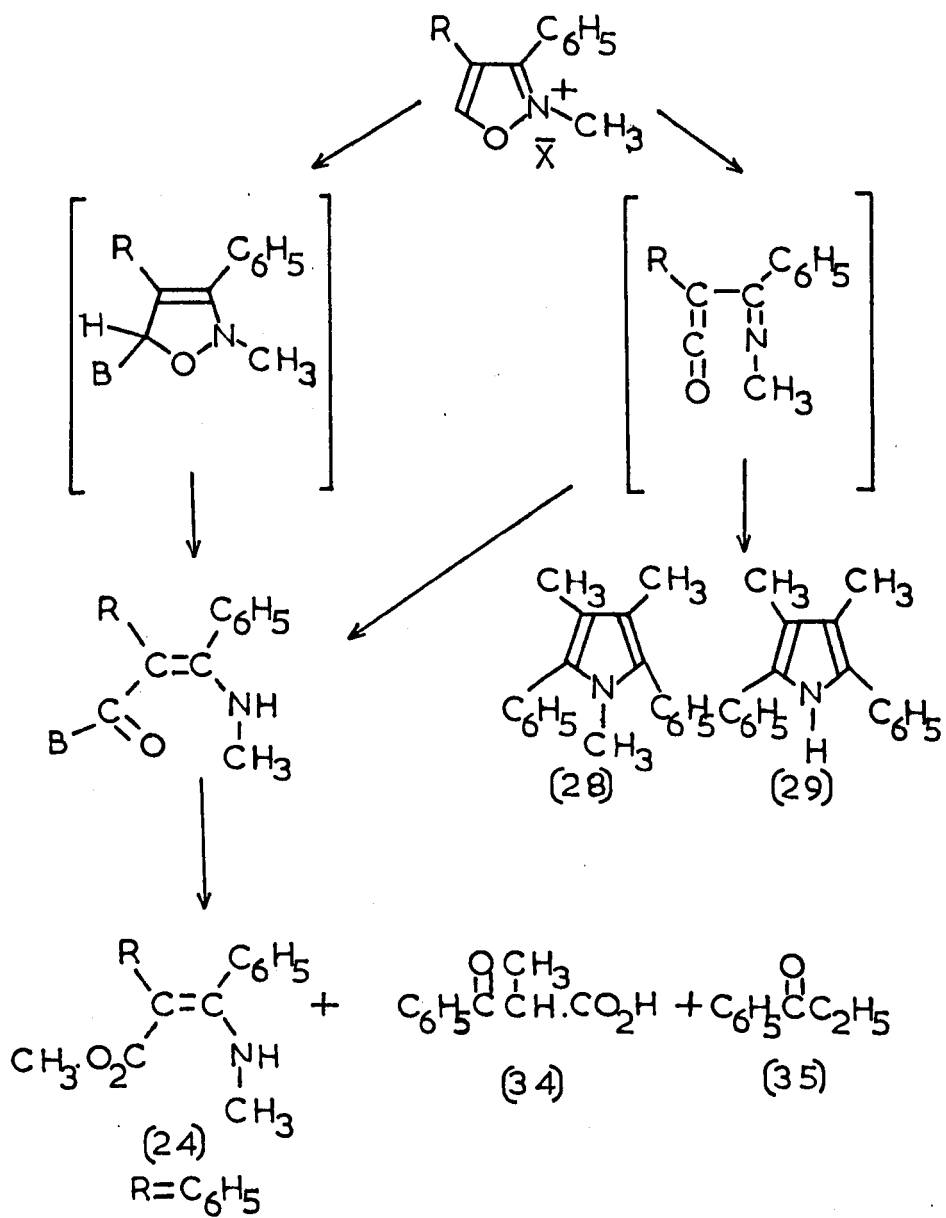
may arise from ketene intermediates as shown by scheme 10.

Although it is not possible to decide which of these pathways is correct some  $\Delta^3$ isoxazolines have been isolated<sup>12</sup> in reactions of salt (22) with nucleophiles (e.g. Grignard reagents at low temperatures, and piperidine or morpholine at low temperatures). These isoxazolines revert back to compounds of type (22) when treated with perchloric acid. The reactions of these isoxazolines are summarized in scheme 11.

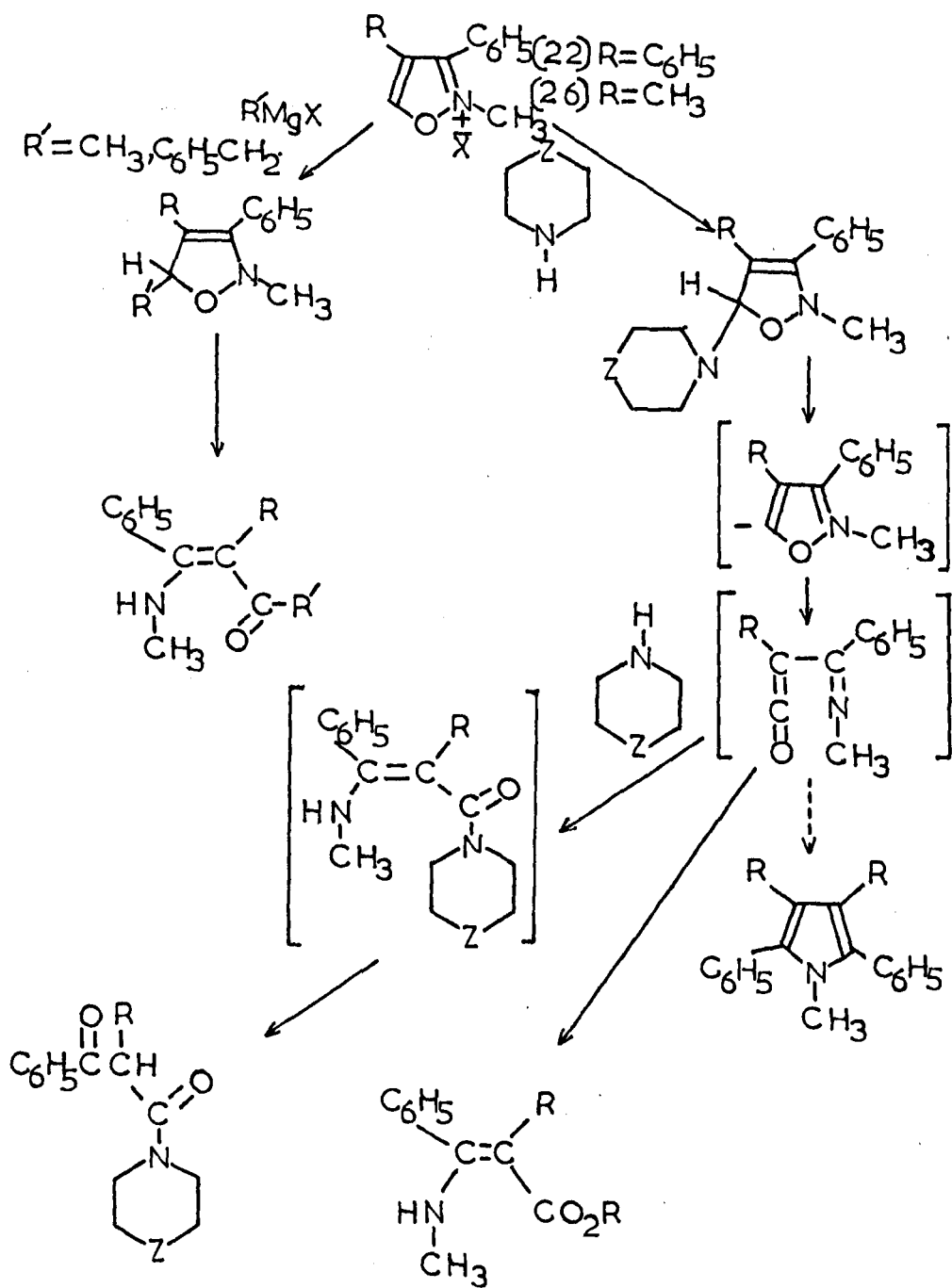
The isoxazolium salts of type (22) react with compounds containing active methylene groups<sup>13</sup> and reaction scheme 12 summarizes the results obtained. The yields shown are those obtained from equimolar quantities of reactants. The structures of pyridones (36) and (37) were assigned by infrared, ultraviolet, nuclear magnetic resonance and unambiguous synthesis.

From experiments in which the yields of products were studied it was noted that an excess of sodium alcoholate decreased the yield of pyridone (36) whilst using a large amount of the sodium salt of the active methylene compound decreased the yield of the enamine (38) and increased that of the pyridones (36) and (37). From this it was deduced<sup>13</sup> that the formation of each product may depend on the strength of the base used.

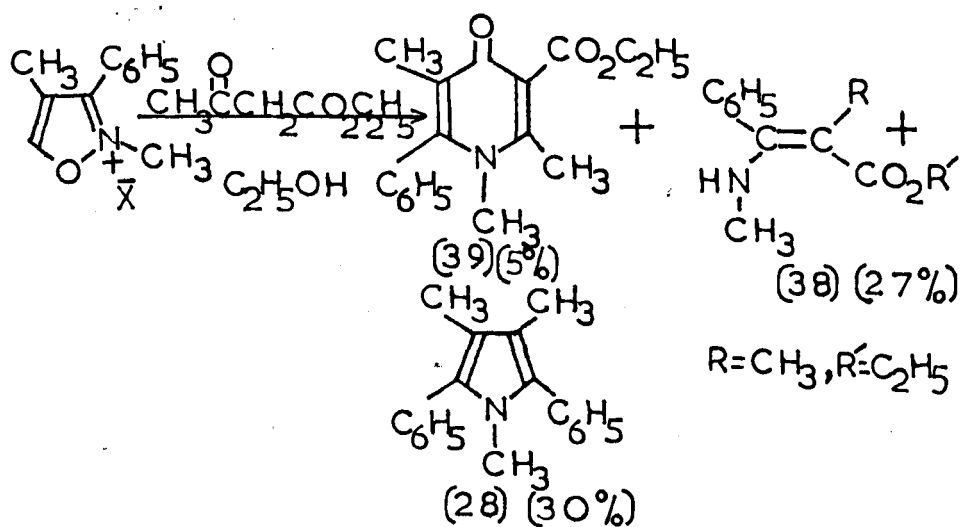
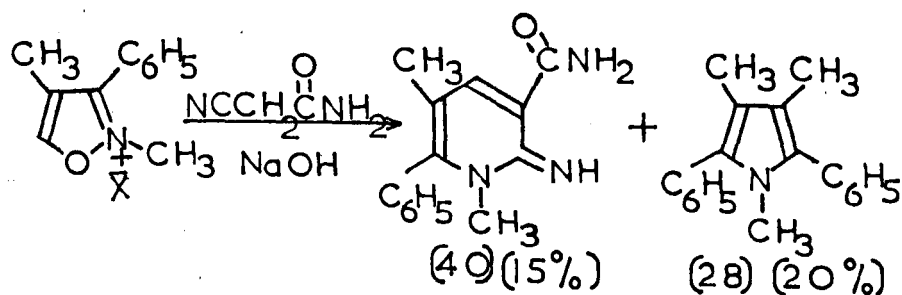
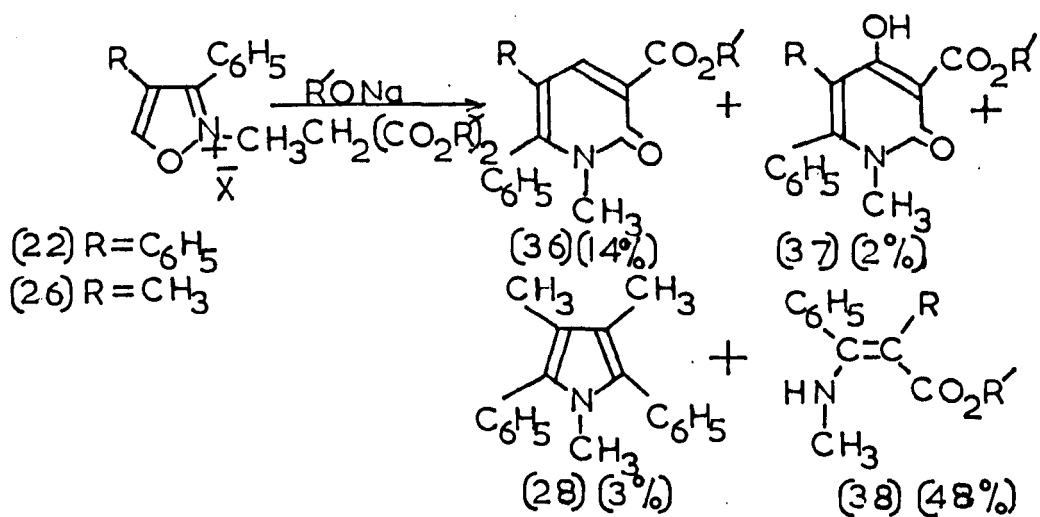
# Scheme 10



# Scheme 11

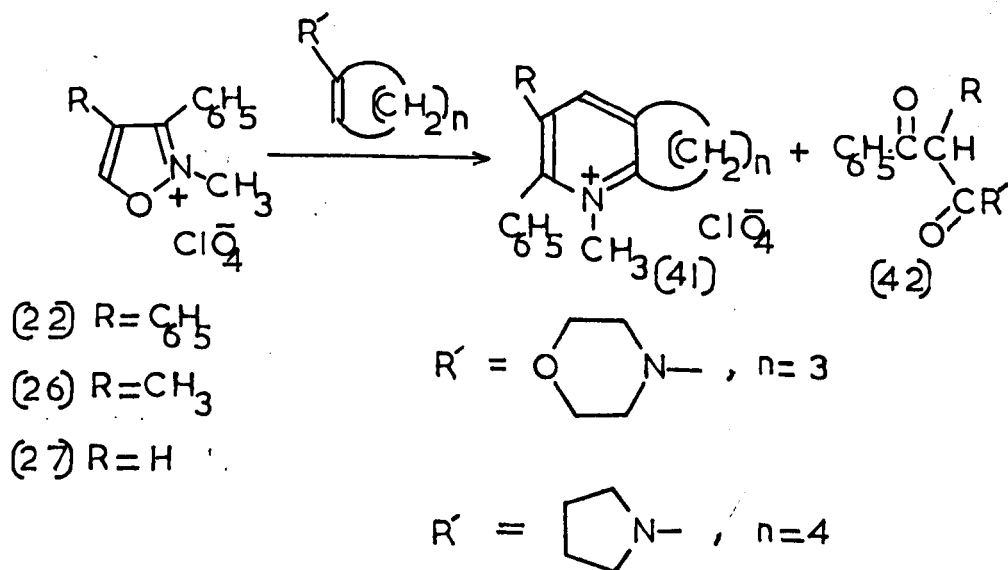


# Scheme 12

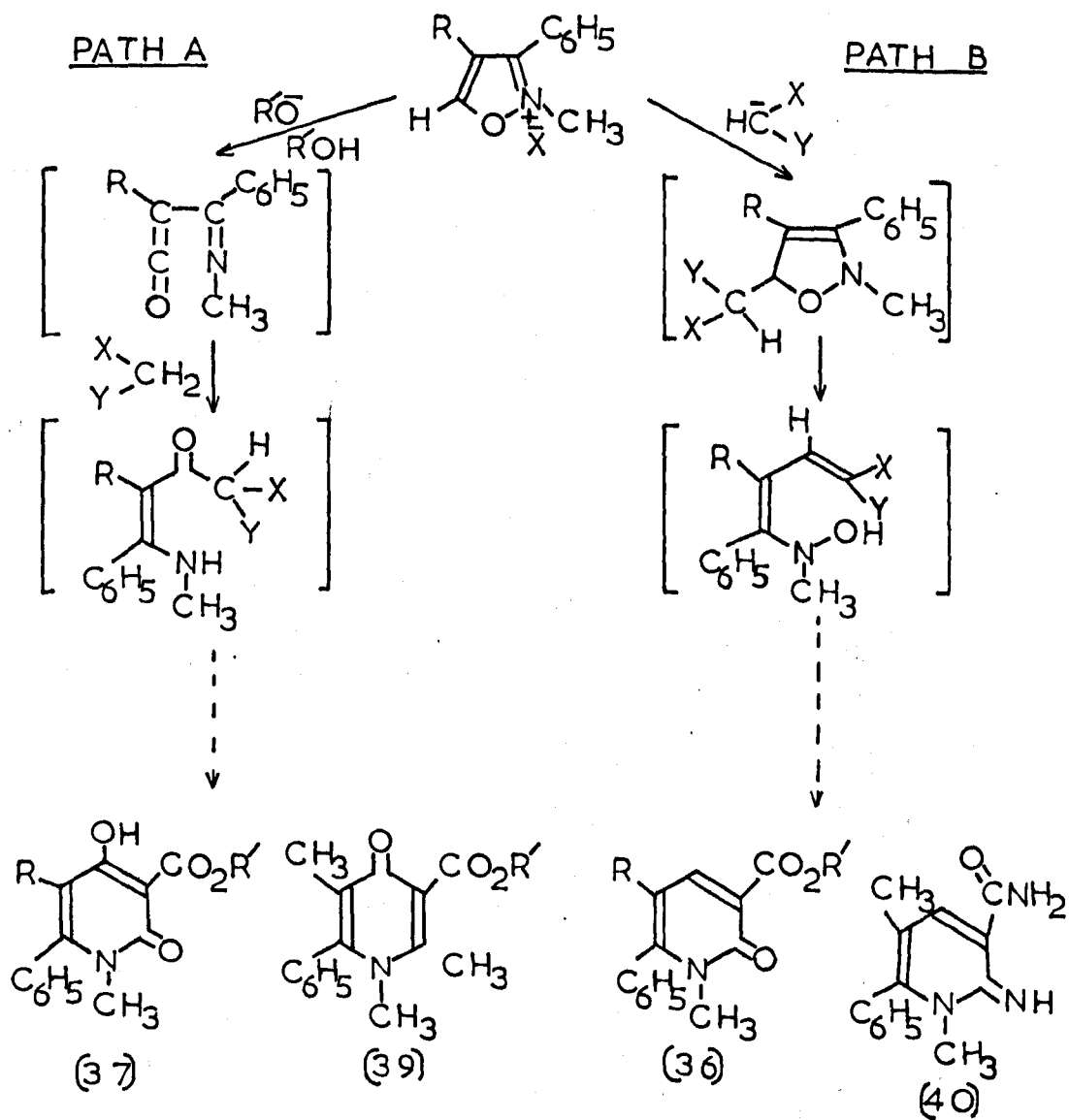


In the presence of a strong base the mechanism may proceed via a ketene; addition of anions to this would then give the pyridones (37) and (39) along with the enamine (38). In reactions with a relatively weak base addition of the nucleophile to C<sub>5</sub> followed by ring opening and ring closure to give the 4-unsubstituted pyridine derivatives (36) and (40) may occur (see scheme 13).

(ii) Reaction with cyclic enamines;<sup>13</sup> the reagents used were 1-morpholino cyclopentene and 1-pyrrolidino cyclohexene. The structures of the products that were obtained were in general proved by spectroscopic data. The formation of the bicyclic salt (41) can be arrived at via pathway B of scheme 13 but a Diels Alder type of mechanism can not be ruled out. The amide (42) may arise by a mechanism following pathway A similar to that of reactions of salts of type (22) with amines.

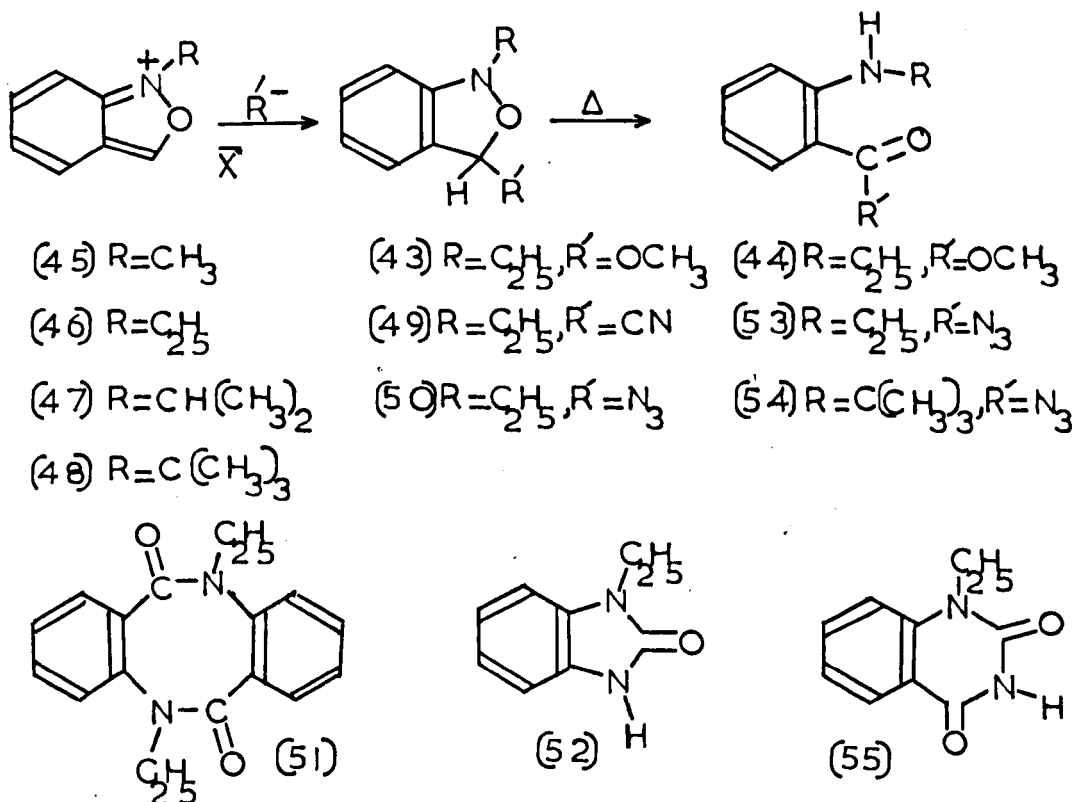


# Scheme 13



(iii) The reactions of isoxazolium salt (26) with potassium cyanate and phenyl hydrazine<sup>13</sup> are summarized in scheme 14.

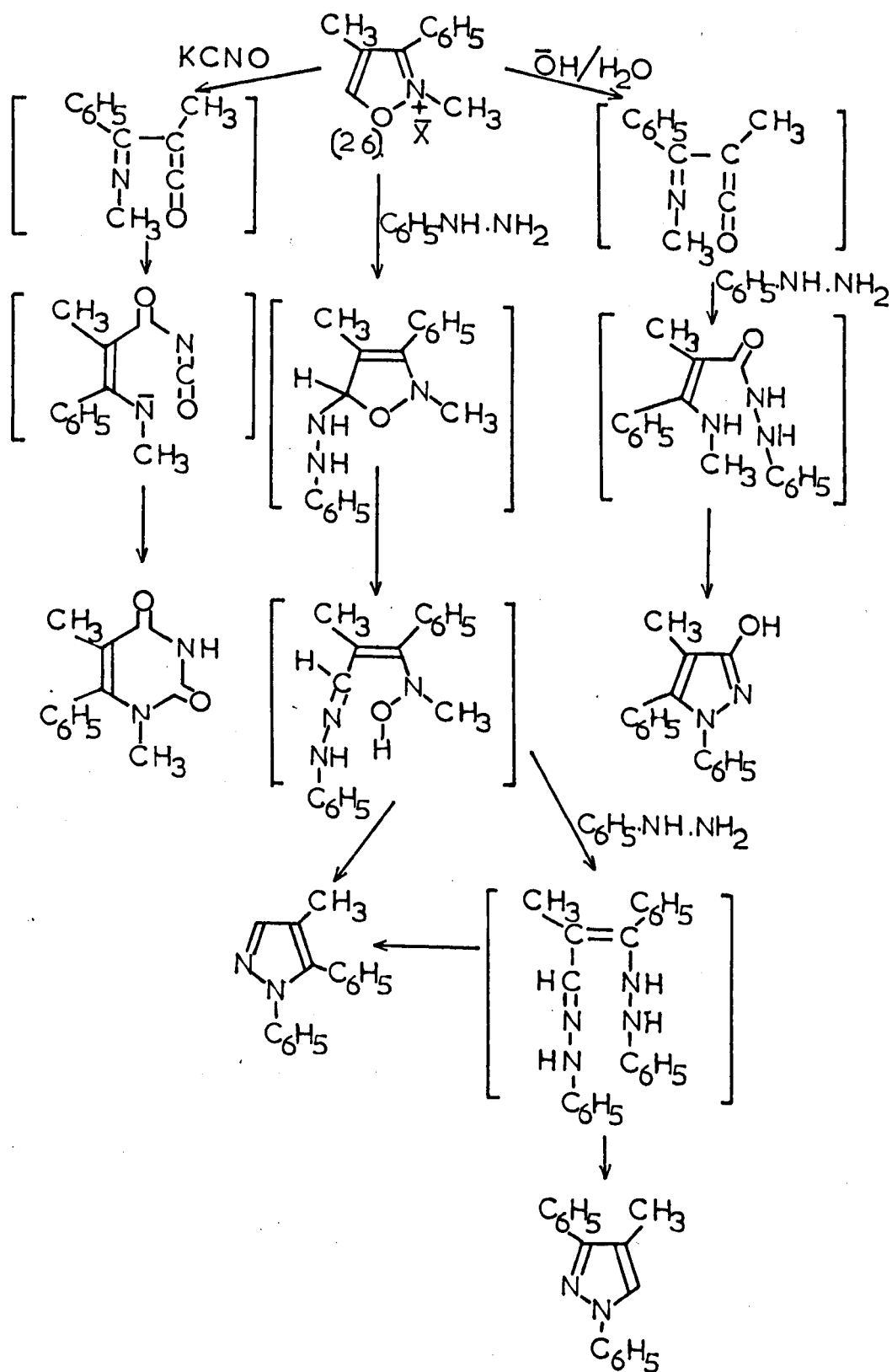
So far the reactions of monocyclic 5-unsubstituted isoxazolium salts have been discussed; some work has also been done on the anthranilium salts. These are easily prepared by alkylation of anthranil with oxonium, carboxonium ions or t-butanol/perchloric acid mixtures.<sup>14</sup> They react cleanly with many anions to give the simple C<sub>3</sub> addition products.<sup>14</sup>



For example the ethyl salt (46) gives the isoxazoline (43) on treatment with methanolic triethylamine, similarly with sodium azide giving the azido-isoxazoline (50) and with sodium cyanide giving the cyanoisoxazoline (49). In



# Scheme 14

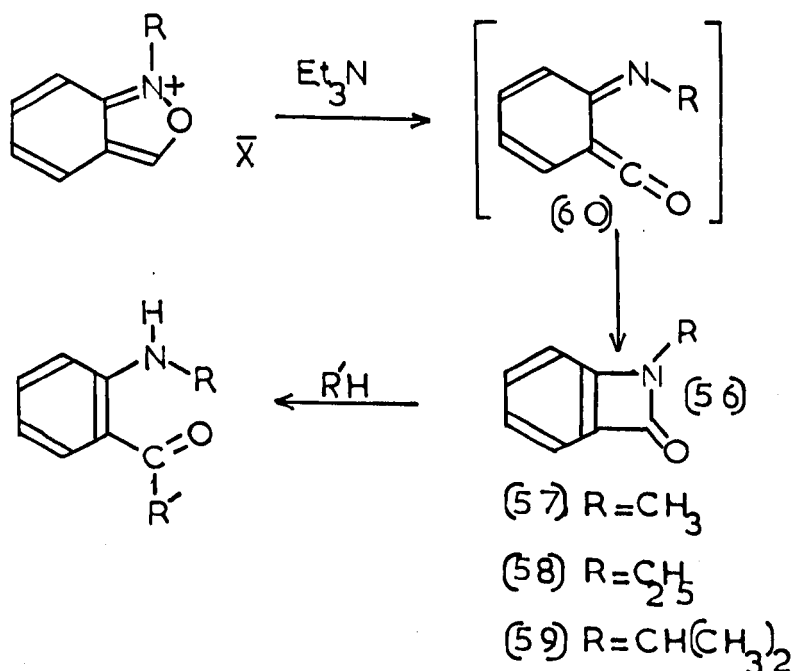


the last two reactions the products rapidly separate out as oils. Thermal conversion of the isoxazolines into compounds of type (44) also occurred in these last two cases but additional products were also observed. e.g. the isoxazoline (43) was converted into the ester (44) on heating under reflux in xylene, however the dimer (51) was also produced.<sup>14</sup> The dimer (51) was the only isolable product from the thermolysis of the cyanoisoxazoline (49). On boiling in carbon tetrachloride the azide (50) was cleanly converted to the benzimidazolone (52); this product would be anticipated from a Curtius rearrangement of an initially generated acyl azide (53).<sup>14</sup> Direct spectroscopic evidence for the acyl azide (54, infrared. 4.67, 6.04 $\mu$ ) was available. In another example the known quinazoline (55) was made in a 60% yield by heating the salt (46) with sodium isocyanate in acetonitrile.<sup>14</sup>

The thermally unstable but isolable acyl azide (54) and other compounds where the azide group is replaced by other nucleophiles can be synthesized directly from the appropriate anthranilium salt at room temperature by titrating the salt in dichloromethane with one equivalent of triethylamine or diisopropyl ethylamine followed by addition of the conjugate acid of the nucleophile (R'H).<sup>14</sup> Spectroscopic evidence (infrared 5.5 - 5.6 $\mu$ , strong) implied that the species obtained in the first step of this procedure was the benzazetinone (56). At 25°C solutions of the azetinones (57) and (58) were unstable

whilst the azetinone (59) was reasonably stable and could be obtained pure in an 80% yield by precipitation of the by-product, triethylammonium perchlorate, with ether followed by vacuum distillation.

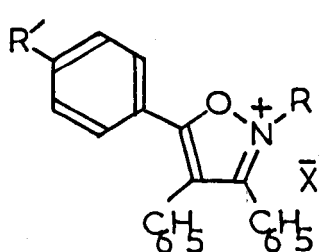
It is believed that the action of triethylamine on the anthranilium salts begins with proton abstraction from C<sub>3</sub> and ring opening to the iminoketene (60) which then cyclizes to the azetinone (56) (similar ring opening reactions are reported for 3-unsubstituted isoxazolium salts).



Although the isoxazolines are excluded as intermediates (from reaction rate and temperature studies) in the reactions of the azetinones (56) to the ring opened compounds of type (44) it is not clear whether the isoxazolines go directly to these ring opened compounds or whether they sometimes involve reversion to the anthranilium salts prior to ring opening.

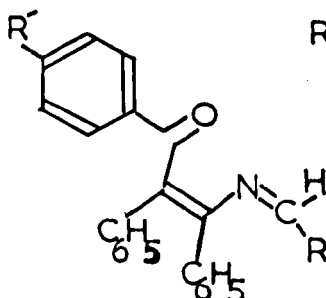
### 3. The 2,3,5-trisubstituted isoxazolium salts.

Kohler<sup>11,15,16,17</sup> was able to isolate products which he called the anhydro derivatives because they had some relation to a postulated intermediate hydrated base, by shaking the salts (61) or (62) with dilute aqueous caustic and extracting the mixture with ether. In his reports he discusses the structures (63), (64) and (65) as possibilities for these products, finally adopting the aromatic ketone (63) as the most satisfactory. In their final paper, Kohler et al describe the preparation of the anhydro derivative from the benzisoxazolium salt (68) to which they assigned the structure (71).



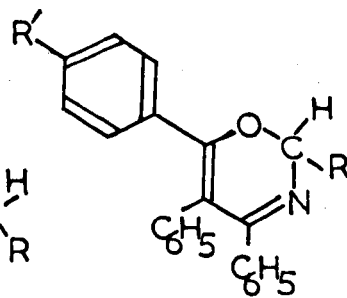
(61)  $R = \text{CH}_3, R' = \text{H}$

(62)  $R = \text{C}_2\text{H}_5, R' = \text{Br}$



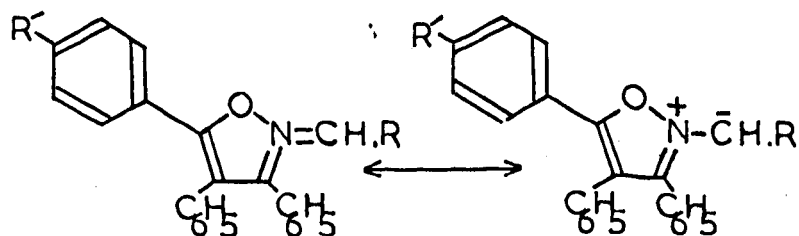
(63)  $R = \text{H}, R' = \text{H}$

$R = \text{CH}_3, R' = \text{Br}$



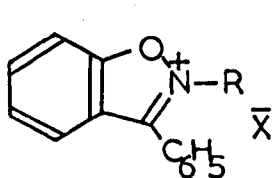
(64)  $R = \text{H}, R' = \text{H}$

$R = \text{CH}_3, R' = \text{Br}$



(65)  $R = \text{H}, R' = \text{H}$

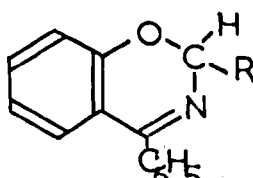
$R = \text{CH}_3, R' = \text{Br}$



(66)  $R = CH_3$

(67)  $R = CH_2CH_3$

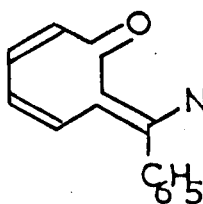
(68)  $R = C_2H_5$



(69)  $R = H$

(70)  $R = C_6H_5$

(71)  $R = CH_3$



(72)  $R = H$

(73)  $R = C_6H_5$

18

King and Durst have prepared the salts (61), (66) and (67) as their chloroferrates and perchlorates and obtained crystalline anhydro derivatives by the Kohler procedure. In addition to the previously proposed structures, the cyclic ketones (72) and (73) are also possible.

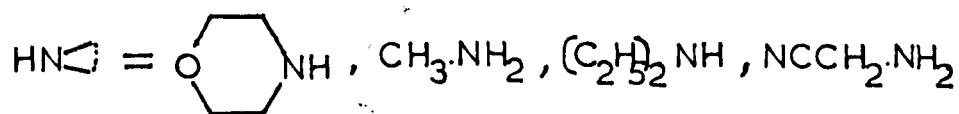
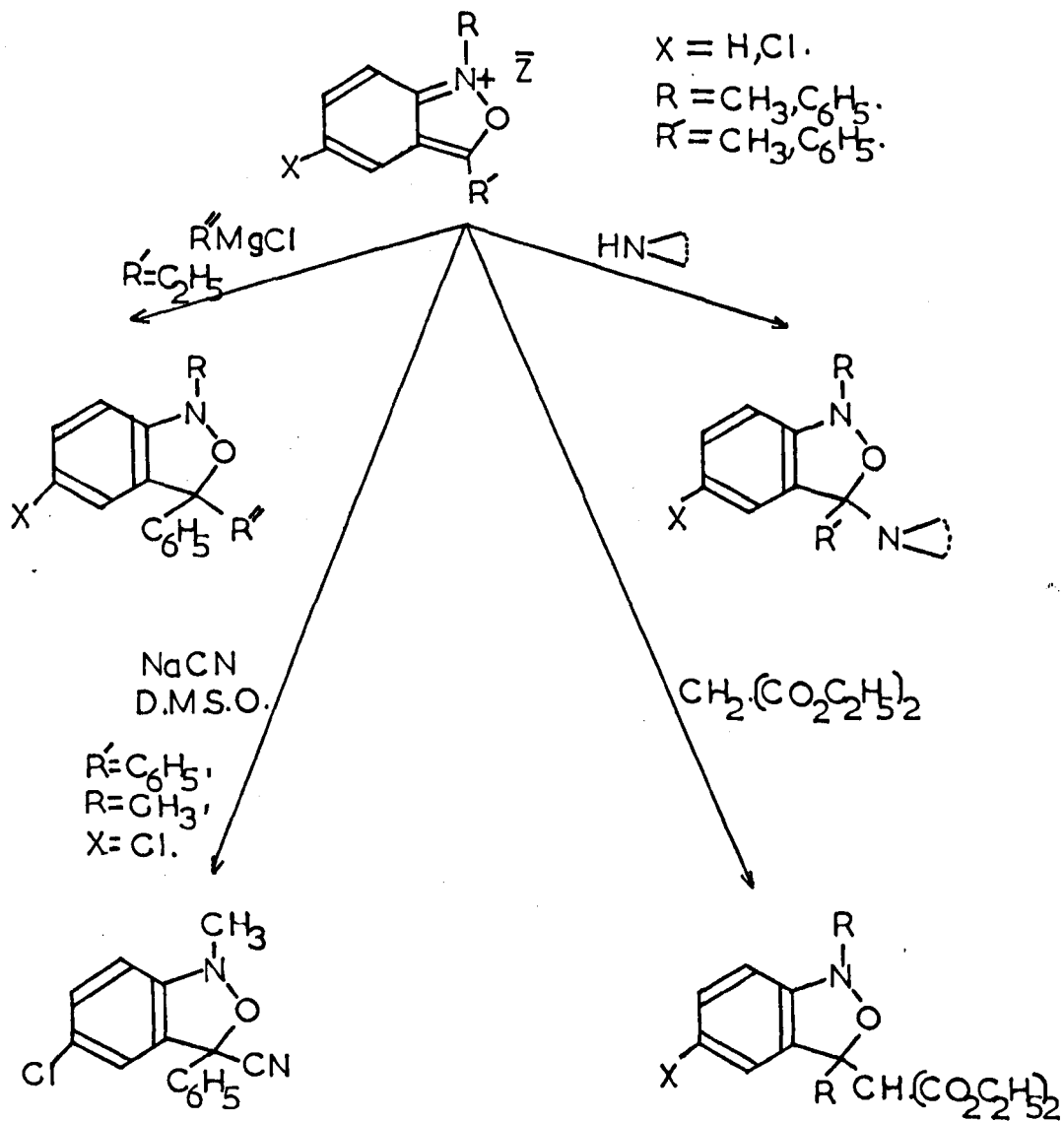
Structure (65) can be ruled out since it requires that nitrogen have ten valence electrons or appear in the form of an ylide which would be much too unstable to be isolated under the reaction conditions.

The single infrared absorption ( $\sim 1620 \text{ cm}^{-1}$ ) shown by these products is in accord with the structures (64), (69), (70) and (71) (c.f. benzophenone anil,  $1623 \text{ cm}^{-1}$  for the  $C = N$  stretching absorption). The open chain structures (63), (72) and (73) would be expected to have

two absorption bands in this region. The ultraviolet absorption data also agrees well with these structures and even though there are few model systems with which to compare the nuclear magnetic resonance data these cyclic structures (64), (69), (70) and (71) seem to be the most satisfactory.

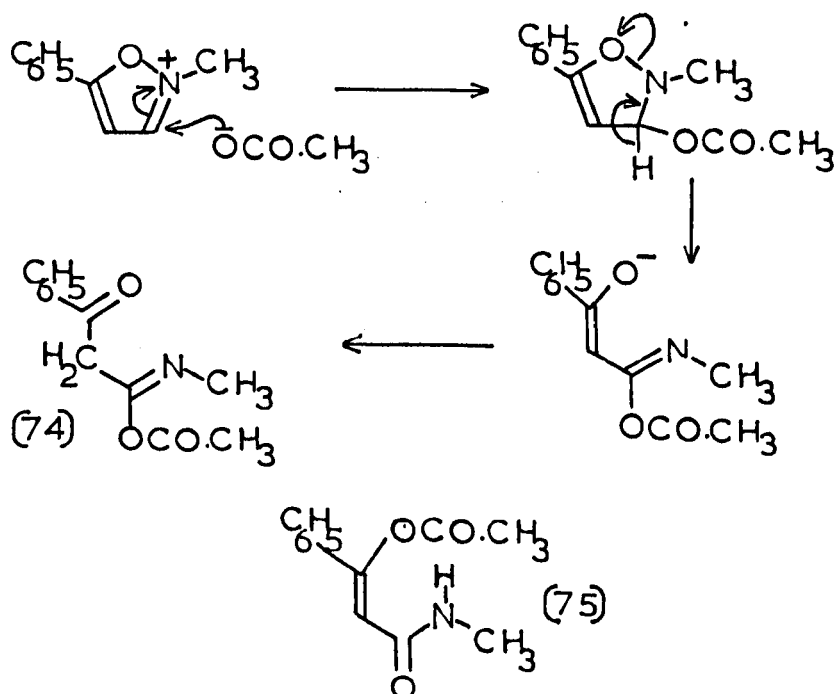
Recently it has been shown<sup>19</sup> that the 1,3-disubstituted 2,1-benzisoxazoles react with some nucleophiles to yield 3-substituted-2, 1-benzisoxazolines; these reactions are summarised in scheme 15.

# Scheme 15



Uses in peptide synthesis.

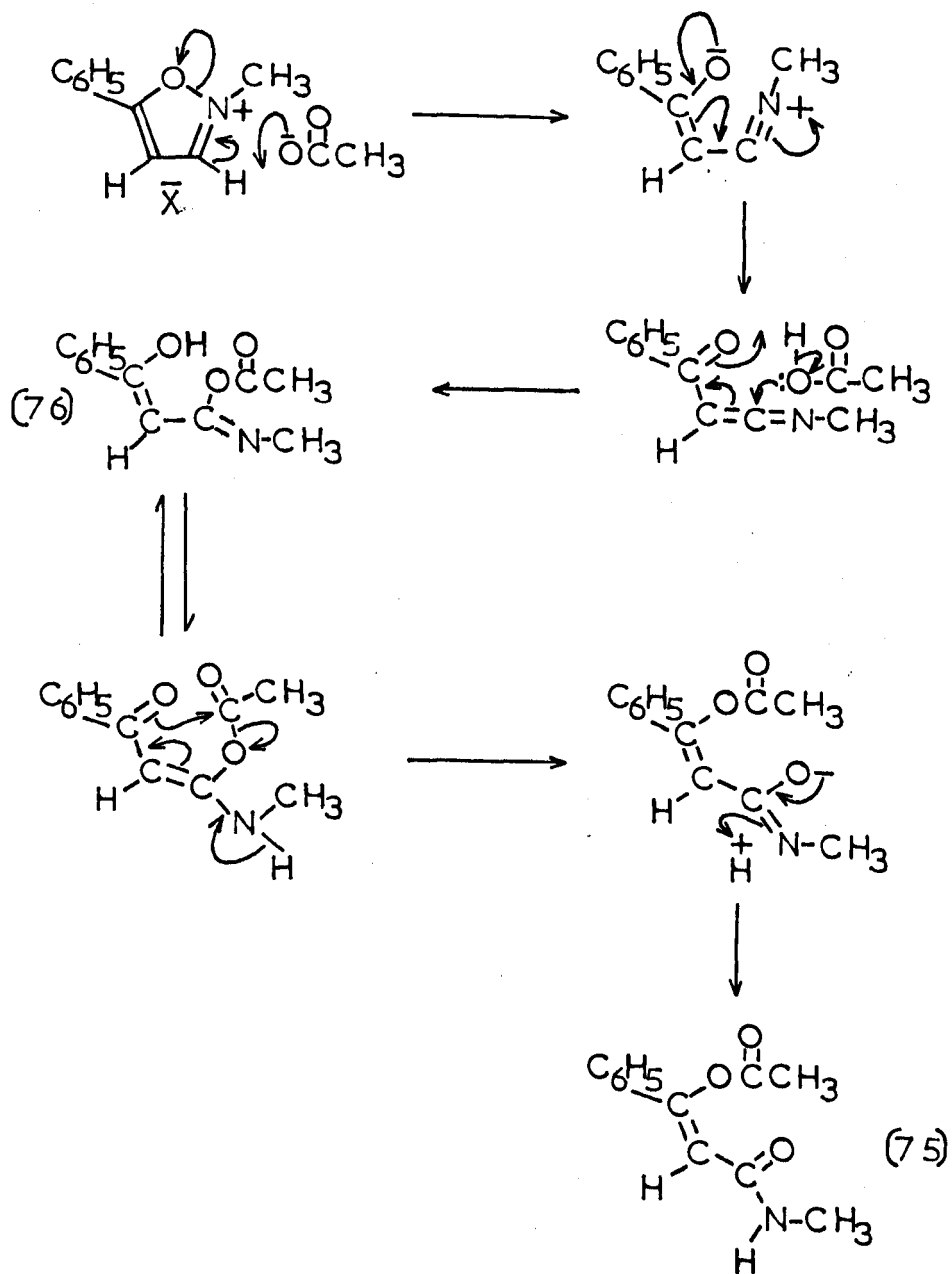
The initial discovery of the reaction of isoxazolum salts with acetate anions was due to Mumm and co-workers in 1902. They believed that the reaction proceeded through a pseudo base followed by ring opening to the imino anhydride as shown below:-



The actual product has now been shown to be the enol ester (75).<sup>20</sup> Most of the recent work is due to Woodward, Olofson and co-workers<sup>9, 20, 21, 22, 23, 24, 25, 26.</sup> who have reported that the reaction proceeds as shown in scheme 16. They have found that nucleophiles abstract the proton attached to C<sub>3</sub> to give the  $\alpha$ -ketoketenimine (which was shown by using triethylamine as the nucleophile), this intermediate has a strong infrared absorption in the cumulative bond region (4.85 $\mu$ ) which disappears very rapidly on the



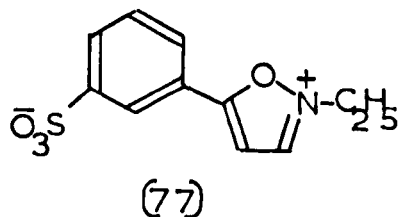
# Scheme 16



addition of acetic acid to yield the enol ester (75). The initial reaction with the acetic acid gives the imino-anhydride (76) which tautomerizes to the ketoform and then rapidly rearranges to the enol ester (75).

The above reaction sequence was to be used in the activation of protected amino acids or peptides<sup>21</sup> in the eventual production of proteins or peptides of a higher molecular weight. The initial attempts to activate the carboxylic acid group of amino acids by this method were not successful due to an unfortunate choice of solvents.<sup>23</sup> For example the triethyl ammonium salt of carbobenzoxyglycine was treated with the isoxazolium salt in an aqueous medium, but the enol ester which precipitated was contaminated by large quantities of carbobenzoxyglycine. When ethanol was used as a solvent the major product was the imino ether derived from addition of ethanol to the intermediate ketenimine.

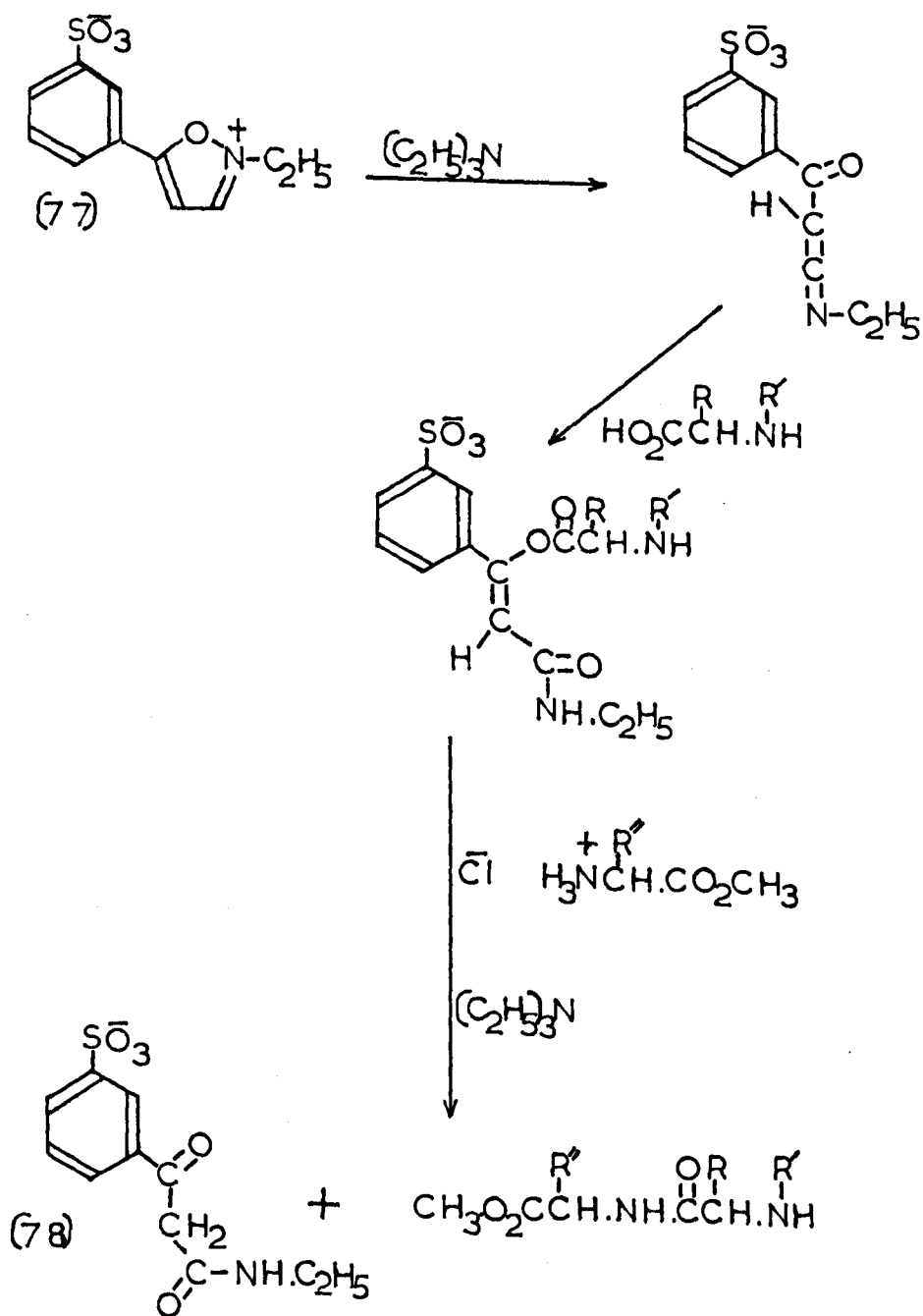
Many alterations to the groups attached to the isoxazolium salt can be made and by so doing one can alter the reactivity and physical properties of the reagent<sup>27</sup> and the active enol ester. One of the most useful salts so far discovered is the zwitterion or internal salt (77) known as Woodward's reagent 'K'.

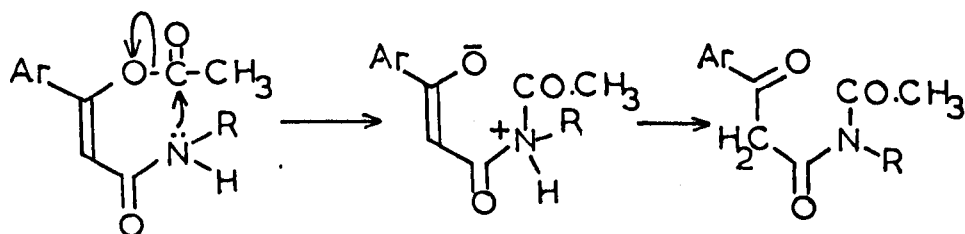


The preparation of proteins may be divided into three distinct stages, activation of the amino acid, combination of this active acid with another amino acid or peptide and finally isolation of the new peptide. The first two stages are shown in scheme 17, isolation of the peptide is usually a simple matter since the by-product (78) is easily removable by trituration with water in which compound (78) is very soluble.

One of the problems arising out of the use of isoxazolium salts as activating agents is that there is a side reaction which although does not occur to a large extent is sufficient to stop the yield being quantitative.<sup>28</sup> A lot of work has been carried out to try and prevent this side reaction; it is a rearrangement of the enol ester to an inert imide.

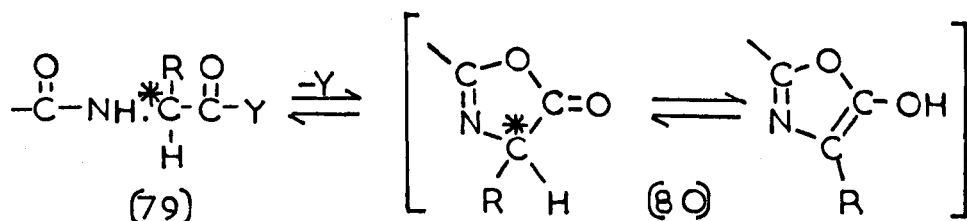
# Scheme 17



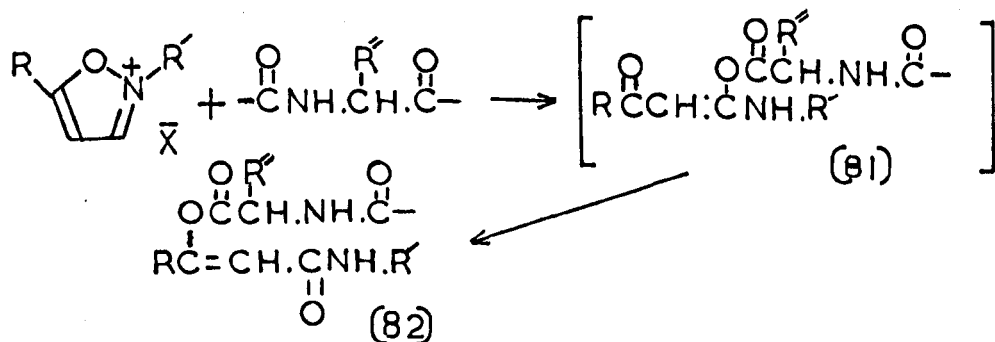


This rearrangement decreases if the N-alkyl group R is changed from a methyl to an ethyl group, which indicates that if this alkyl group could be a larger one the side reaction may disappear altogether. An aryl group has been tried in this position<sup>24</sup> and this surprisingly increased the amount of the imide produced. The rearrangement is base catalysed and it is easier to deprotonate an anilide than the N-alkyl amide which in fact increases the rate of imide production. When R is changed to t-butyl the O $\rightarrow$ N migration is eliminated,<sup>25</sup> unfortunately the t-butyl ketenimine is so unreactive that it does not easily yield enol esters with peptide acids.

A slight amount of racemization of the resultant peptide has been noticed when using Woodward's reagent (77).<sup>26</sup> The common mechanism for racemization during peptide synthesis involves fragmentation of an acylating agent (79) from a peptide acid to give an azlactone or oxazolone (80).<sup>34</sup>



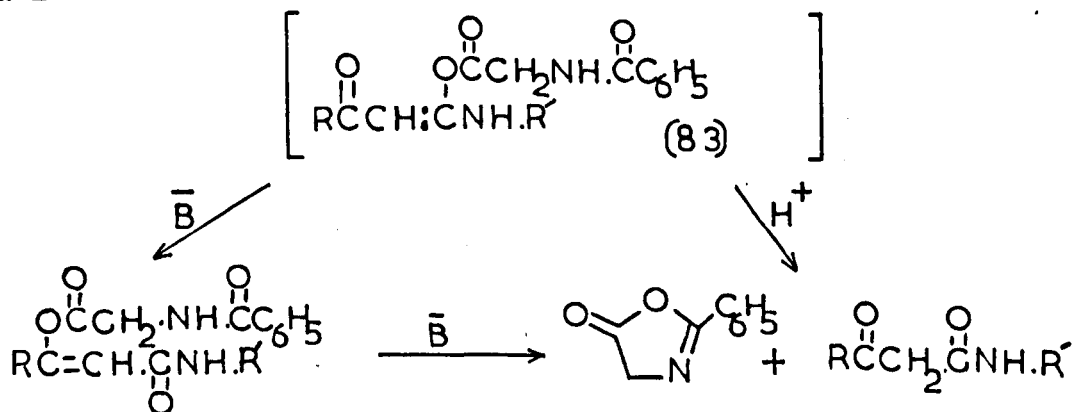
Because of its keto and enol forms the azlactone (80) causes racemization of the asymmetric carbon. Because of the favourable racemization results obtained with Woodward's reagent it appears likely that decomposition of the ester (81) to the azlactone is not as rapid as its rearrangement to the enol ester (82).



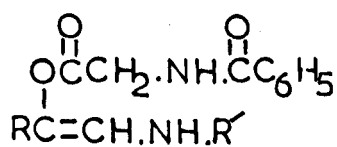
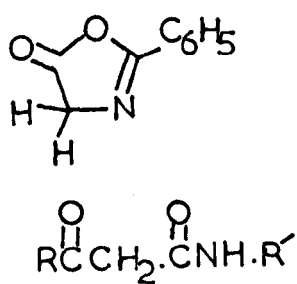
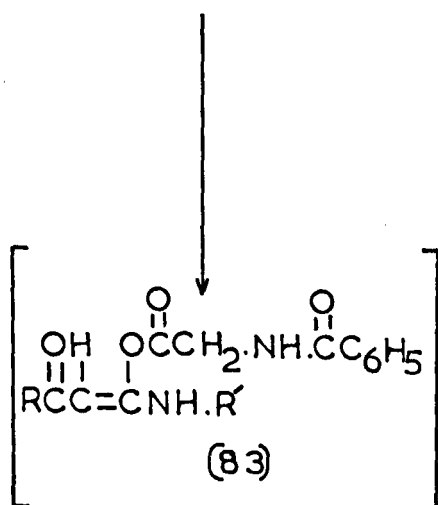
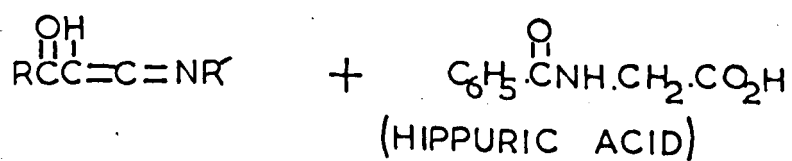
Infrared spectral studies of the reaction of hippuric acid with a variety of isoxazolium salts shows that the enol esters prepared in general are complicated by azlactone formation.<sup>26, 28</sup> (See scheme 18). The fact that the reaction course depends on the pH. of the medium may be used to explain why only reagent (77) gave the enol ester almost entirely free from racemization. The main difference between the salt (77) and others is that it is a zwitterion which is relatively insoluble in acetonitrile. All the other isoxazolium salts dissolve immediately with rapid ring opening to give the

ketoketenimine and hippuric acid which then combine in the slow step of the reaction. In contrast the zwitterion (77) dissolves so slowly that the rate of solution is rate determining and the acid and ketoketenimine do not build up in detectable quantities. This means that whilst other salts decompose in a medium containing acid generated by the fast ring opening to give azlactone, the intermediate (83) from salt (77) is exposed to unconsumed base which favours the formation of the enol ester. This can be shown to be correct by first reacting the inner salt (77) with triethylamine and then coupling the ketenimine with hippuric acid ( this means that the reaction medium has a similar pH. to that attained using other isoxazolium salts); azlactone formation does then occur to an appreciable extent.

The indication is that azlactone formation from the intermediate (83) is acid catalysed whilst the enol ester formation from this intermediate is base catalysed. However the base concentration can not be greatly increased since the enol ester itself decomposes to azlactone under more strongly basic conditions.



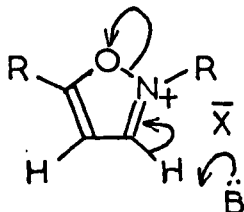
# Scheme 18





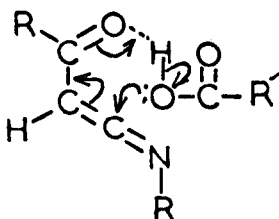
There is evidence for the following in the mechanism of the activation of carboxylic acids:-

- (i) Proton abstraction from  $C_3$  by base.<sup>20, 23, 28</sup>  
 (ii) Anticlockwise movement of the electrons during ring opening.<sup>20, 23, 28</sup> i.e.



- (iii) That there exists an  $\alpha$ -ketoketenimine intermediate.<sup>20, 23, 28</sup>

- (iv) The intermediate reacts with the carboxylic acid rather than the anion.<sup>20, 23, 28</sup> i.e.



- (v) The structure of the enol ester.<sup>20, 23, 28</sup>

The advantages of the system described are that the product yield is very high, all the by-products are water soluble and that there is little or no racemization under optimum conditions. However Woodward's reagent 'K' is very expensive to produce, the side reaction means that although the yields are high they can not be

quantitative, there is some racemization under useful reaction conditions and there is a limited choice of solvent in which to carry out the reaction.

Uses in photography.

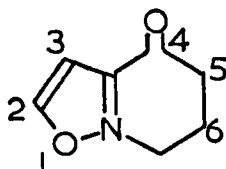
Isoxazolium salts can be incorporated into gelatin silver halide photographic emulsions and when they are, they improve the abrasion resistance, the adhesion to supports,<sup>29,30.</sup> the resistance to swelling by aqueous solutions<sup>31, 32, 33.</sup> and have an antifoggant activity.

The improvement in the above properties of the emulsions arises because the isoxazolium salts assist in the cross-linking process between amino and carboxyl groups of adjacent gelatin chains.<sup>27</sup>

## Discussion.

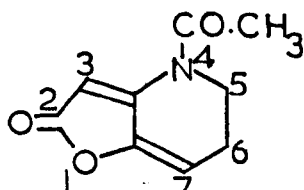
### (i) Introduction.

The isoxazolium salts dealt with in most detail have the general formula and nomenclature shown below:-

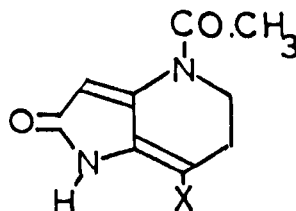


4,5,6,7-Tetrahydro-4-oxoisoxazolo [2,3-d]  
pyridinium bromide

The rearrangement products obtained from these bicyclic salts have the following general formulae and nomenclature:-

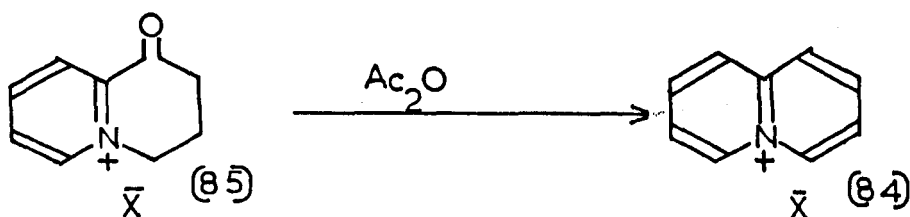


4-Acetyl-5,6-dihydro-4H-  
furo [3,2-b]pyrid-2-one



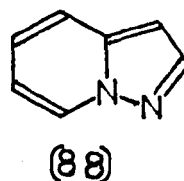
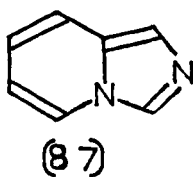
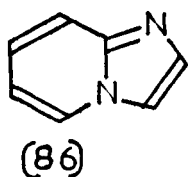
4-Acetyl-7-halogeno-5,6-dihydro-  
4H-pyrrolo[3,2-b]pyrid-2-one

The preparation of the quinolizinium salt (84) <sup>35, 36</sup> has shown the stability of the ten  $\pi$  electron system which has a nitrogen atom at the bridgehead. The Glover and Jones <sup>36</sup> method involved the synthesis of the ketonic salt (85) which aromatized on heating in acetic anhydride. The mechanism of this aromatization step has been considered and is dealt with in detail later (p. 51.)

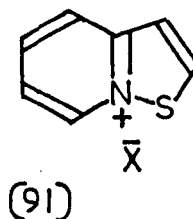
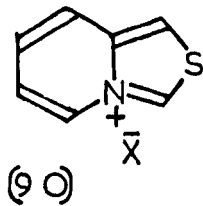
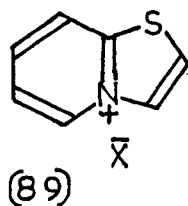


Because of the aromatic character and interesting electronic distribution of these salts the preparation of isoelectronic systems has been considered. By substitution of a two carbon fragment for an hetero atom a series of salts can be envisaged which contain five and six membered rings fused together.

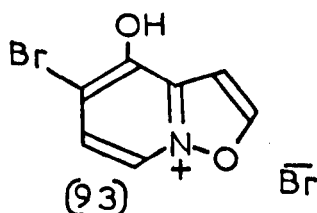
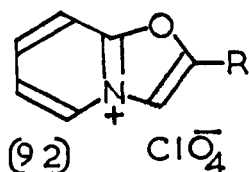
All three nitrogen analogues (86)<sup>37</sup>, (87)<sup>38</sup> and (88)<sup>39</sup> are known but they are preferentially prepared as the free bases rather than the pyridinium salts.



Of the possible three thiazolo pyridinium salts (89)<sup>40,41,42,43</sup>, (90)<sup>43</sup>, (91) the only one which has not been prepared is the isothiazolo [2,3-a] pyridinium salt (91).



Of the analogous series where the sulphur is replaced by oxygen only the oxazolo[3,2-a]pyridinium (92)<sup>44, 45</sup> and the isoxazolo[2,3-a]pyridinium (93)<sup>46</sup> salts have been prepared.



#### (11) Furopyridones.

Prior to the reported preparation of the substituted isoxazolo[2,3-a]pyridinium salt (93) an attempt was made to prepare the parent compound by an extension to the Glover and Jones synthesis of quinolizinium salts. The final step using acetic anhydride as the aromatizing reagent led to the production of an interesting rearrangement product.

The cyclic salt (94) was prepared from 3-carbethoxy isoxazole which was obtained free from the 5-substituted isomer via the isoxazoline. Carbethoxy-chloraldoxime was treated with vinyl acetate and triethylamine which gave 3-carbethoxy-5-acetoxy- $\Delta^2$ -isoxazoline (95). On heating this isoxazoline to between 180-190°C the isoxazole (96) distilled over after a fore-run of acetic acid. An improved yield over the method described above<sup>47</sup> was obtained if a solution of carbethoxy-chloraldoxime in ether was added to a heated solution of vinyl acetate and triethylamine in ether. The yield can be improved

further by heating the crude product from the above reaction to the appropriate temperature.

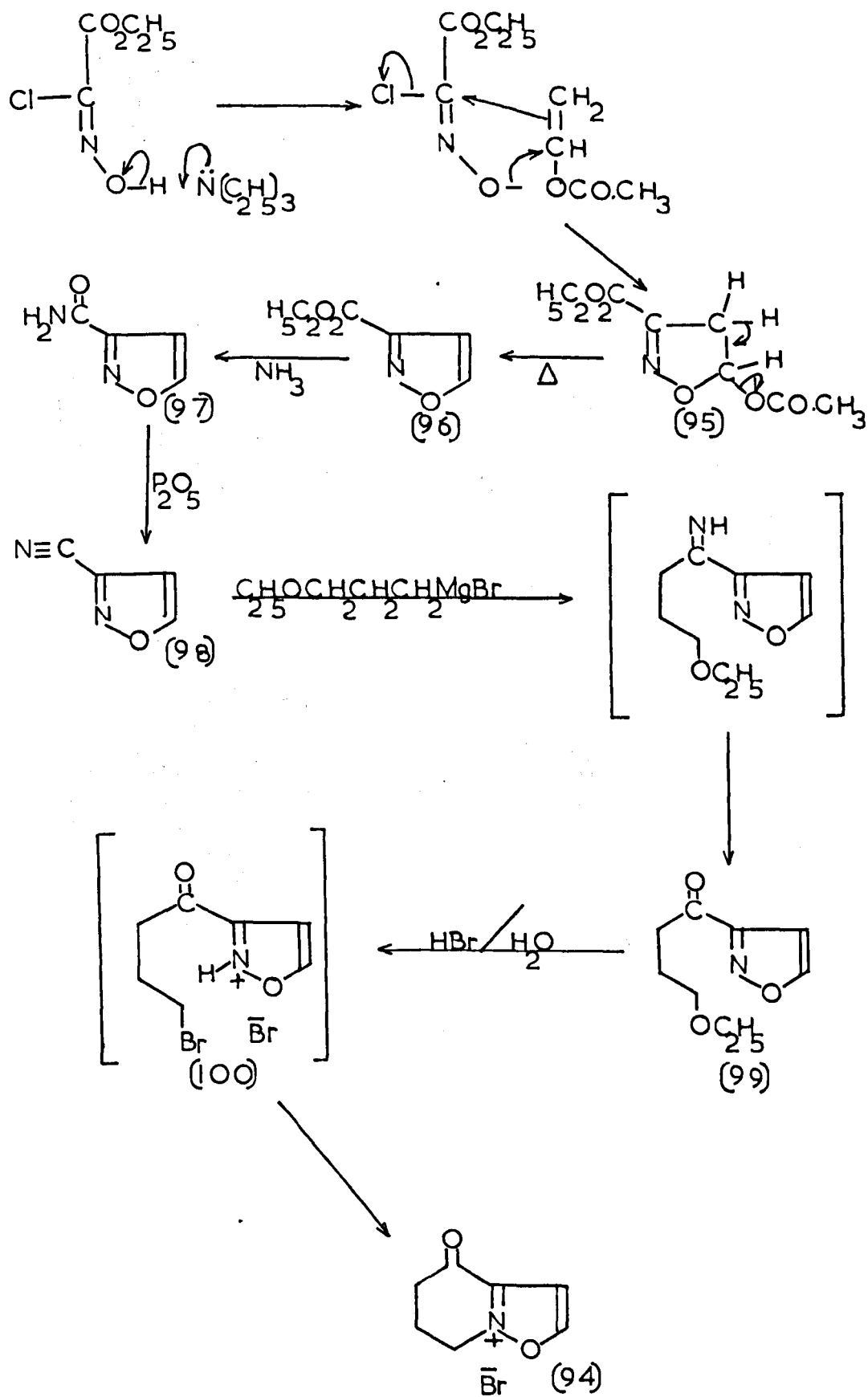
The 3-carbethoxy isoxazole (96) was then treated with an excess of cold ammonia solution to convert the ester into the amide (97). This amide (97) was then dehydrated with phosphorus pentoxide to give the nitrile (98) which reacted with the Grignard reagent from 3-ethoxypropyl bromide to give 3-(4-ethoxybutyryl) isoxazole (99) after hydrolysis of the intermediate imine. The isoxazole (99) cyclised readily on heating in aqueous hydrobromic acid. The final traces of hydrobromic acid which remained after vacuum distillation were removed by adding absolute ethanol and distillation under reduced pressure.

The cyclisation occurs more easily in this system than with the quinolizinium salts because the isoxazole is very much less basic than pyridine. Hence no 3-(4-bromobutyryl) isoxazole hydrobromide (100) was isolated, the hydrogen bromide being lost on distilling off the absolute ethanol in the work-up described above. The reaction sequence is summarised in scheme 19.

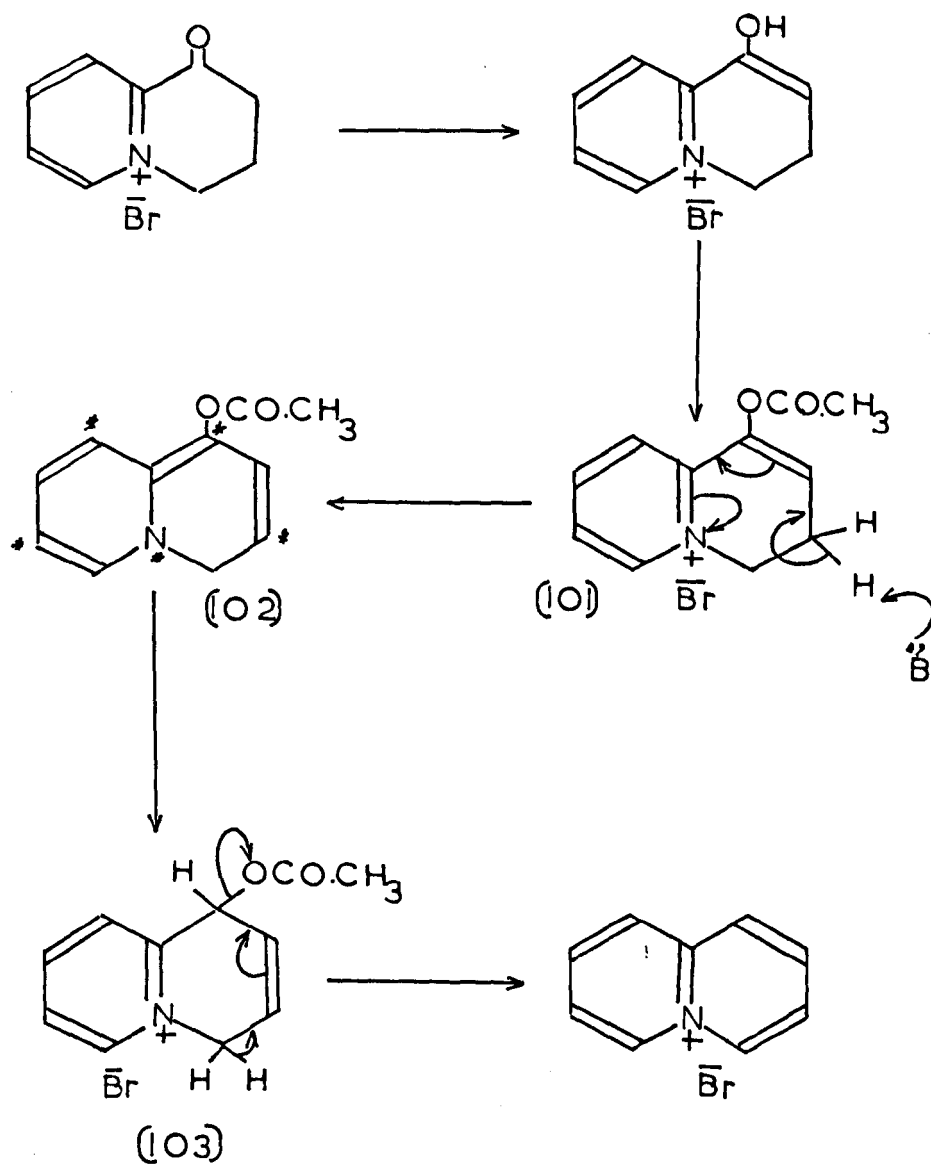
It was hoped that this cyclic ketone (94) would aromatize in a similar manner to that seen in the quinolizinium system, the suggested mechanism of which is shown in scheme 20. The initial step is enolisation of the keto group with subsequent formation of the enol acetate (101) which can lose a proton by base abstraction

..

# Scheme 19



Scheme 20





followed by bond reorganisation to give the quinolizine (102). Protonation of this uncharged intermediate (102) may take place at any of the positions marked. The two most likely positions are 1 and 3 since protonation at the others gives intermediates lacking an aromatic sextet of electrons. Protonation at position 3 regenerates the intermediate (101), protonation at position 1 however yields the salt (103) which can lose acetic acid by a 1,4-elimination to give the quinolizinium salt.

Treatment of the isoxazolium salt (94) with boiling acetic anhydride led to an immediate darkening of the colour of the mixture. After heating the solution for a very short time the acetic anhydride was removed by distillation under reduced pressure. This gave a dark brown oil which was insoluble in water but soluble in organic solvents indicating that the aromatic salt had not been produced. By percolating this oil down an alumina chromatography column with benzene and recrystallizing the resultant solid from benzene, a major product was obtained in 47% yield. The product was a pale yellow solid which showed infrared absorptions at 1778, 1684 and 1590  $\text{cm}^{-1}$ . The mass spectral data and the microanalysis confirmed the formula to be  $\text{C}_9\text{H}_9\text{NO}_3$ . The nuclear magnetic resonance spectrum is given on p.57 and is discussed with regard to the postulated structures shown below.

The remainder of the material apart from a very minor

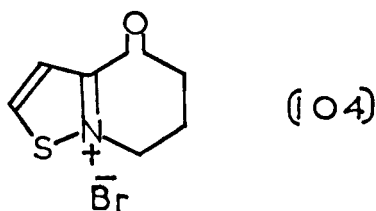
component which was eluted prior to the major product remained at the top of the chromatography column even when the polarity of the eluent was increased. This indicated that it was polymeric in nature (approximately 50% of the total).

Attempts have been made to improve the yield of the rearrangement product. It was assumed that the conditions had to be made milder since when the reaction time in acetic anhydride was increased the amount of polymeric material produced increased very rapidly. Separate samples of the isoxazolium salt (94) were dissolved in acetic acid, acetic acid with one equivalent of acetic anhydride and a 50/50 mixture of acetic acid/acetic anhydride. The solutions were heated under reflux for a short time and the solvent then removed under vacuum but only the starting material was isolated in each case. The lack of reaction may have arisen because of the reduction in the reaction temperature.

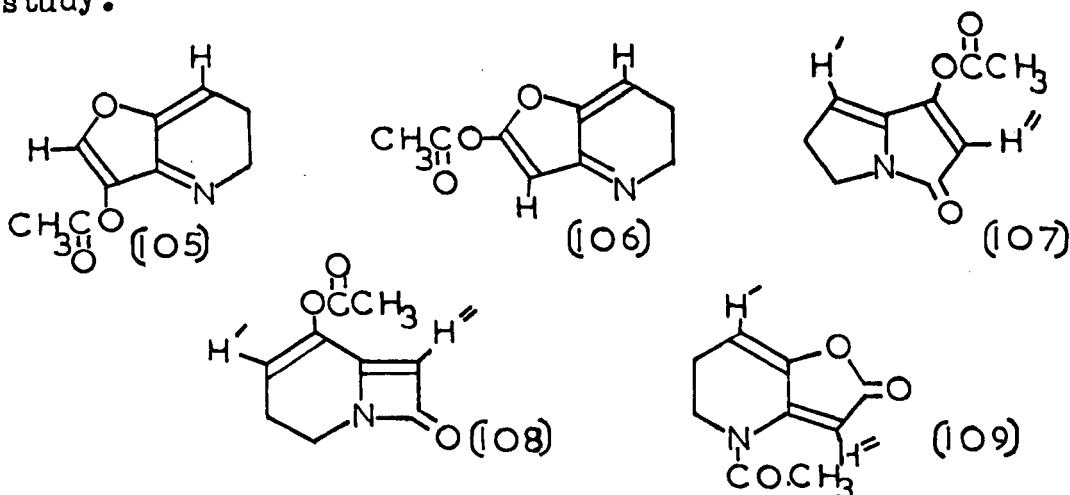
The yield of the product could be increased to 60% by reducing the reaction time. This could best be done by heating the salt (94) in acetic anhydride to its boiling point and then decanting the solution from the undissolved salt. This procedure was then repeated until all of the salt had reacted.

It has been reported by Jones and Jones<sup>48</sup> that the

ketone (104) gave a similar crude product on treatment with acetic anhydride but a pure product was not isolated.



The structures originally postulated for the rearrangement product from the isoxazolium salt (94) are shown below. Along with these is the correct structure (109) which was deduced from an X-ray crystallographic study.



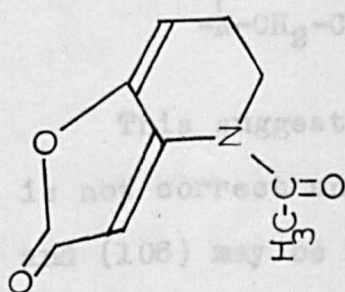
All four postulated structures (105-108) contain the vinyl acetate group which agrees with the proton singlet absorption at  $\delta$  2.34 p.p.m. in the nuclear magnetic resonance spectrum (p.57). This also gives an explanation for the loss of 42 mass units ( $\text{CH}_2\text{CO}$ ) from the molecular ion and for the base peak at 43 m/e in the mass spectrum. This vinyl acetate group was also postulated in order to explain the carbonyl absorption at  $1778\text{ cm}^{-1}$  (normal vinyl ester absorptions occur at approximately  $1760\text{ cm}^{-1}$ )

N.m.r. Spectrum Of

4-acetyl-5,6-dihydro-4H-furo[3,2-b]pyridine-2-one.

evident in the single proton absorptions at 4.6.1 and 5.6 p.p.m. This latter absorption appears as a split triplet ( $J = 5\text{Hz}$ ) suggesting a methine proton next to a methylene group. All the suggested structures have such a proton. The chemical shift of the two triplet absorption at 4.5.6 p.p.m. tends to indicate it is due to a methylene group which is attached to a nitrogen atom and next to another methylene group. This second methylene group would provide the remaining absorption at 2.6 p.p.m. (a two-proton multiplet whose chemical shift may be explained by the deshielding effect of adjacent unsaturation).

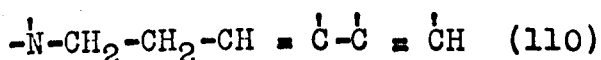
From the nuclear magnetic resonance spectrum we can therefore postulate that the compound contains a fragment of the following structure:-



This suggests that the dihydropyridine (108) is not correct in fact the two dihydropyridines (109) and (110) may be ruled out on chemical evidence. Heating the rearrangement product in xylene with a 10% palladium charcoal catalyst or heating it in xylene in the presence of dichloro-dicyano-1,4-benzoquinone caused no dehydrogenation. It was also expected that these dihydropyridines would act as dienes in a Diels-Alder type of addition.

Structures (107) and (108) have protons H' and H'' which could show the long range coupling of 1 Hz evident in the single proton absorptions at  $\delta$  6.1 and 5.8 p.p.m. This latter absorption appears as a split triplet ( $J = 5\text{Hz}$ ) suggesting a methine proton next to a methylene group. All the suggested structures have such a proton. The chemical shift of the two proton, triplet absorption at  $\delta$  3.9 p.p.m. tends to indicate that it is due to a methylene group which is attached to a nitrogen atom and next to another methylene group. This second methylene group would provide the remaining absorption at  $\delta$  2.6 p.p.m. (a two-proton multiplet whose chemical shift may be explained by the deshielding effect of adjacent unsaturation).

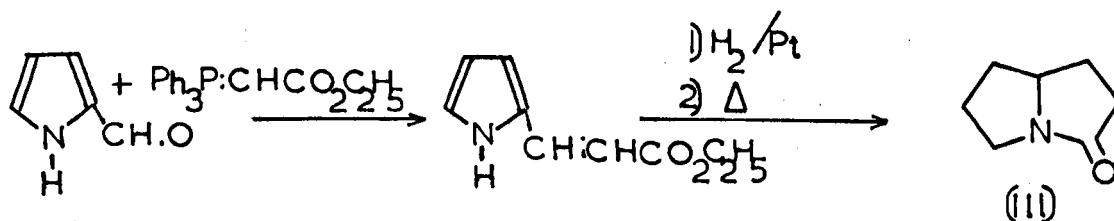
From the nuclear magnetic resonance spectrum we can therefore postulate that the compound contains a fragment of the following structure:-



This suggests that the dihydropyridine structure (105) is not correct and in fact the two dihydropyridines (105) and (106) may be ruled out on chemical evidence. Heating the rearrangement product in xylene with a 10% palladium charcoal catalyst or heating it in xylene in the presence of dichloro-dicyano-1,4-benzoquinone caused no dehydrogenation. It was also expected that these dihydropyridines would act as dienes in a Diels-Alder type of addition.

Heating the compound with dimethyl acetylene dicarboxylate or heating it in the presence of tetracyano ethylene in benzene gave no such addition products. It was possible that these two dienophiles did not react because they were electron deficient and the system required an electron rich dienophile. Heating the rearrangement product with styrene in benzene also failed to produce an adduct. Therefore the two dihydropyridines were considered to be unlikely structures for the product.

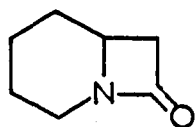
The pyrrolizidone structure (107) agreed with most of the spectroscopic data and here the small ring carbonyl group may be responsible for the infrared absorption at  $1778\text{ cm}^{-1}$ . Good and Jones<sup>49</sup> have prepared the fully saturated, unsubstituted 3-pyrrolizidone (111) from 2-formyl pyrrole as shown below.



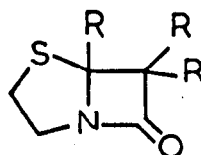
While hydrogenation of the rearrangement product (see p.78) led to a piperidyl acetic acid derivative, hydrogenation of the 3-pyrrolizidone (111) led to complete recovery of the starting material. Kochetkov and Likhoshertov<sup>50</sup> also found that this bicyclic system (111) was stable on attempted reduction with lithiumaluminum hydride. This suggested that if the rearrangement product

had the dihydropyrrolizine structure (107) then on reduction it did not go via the pyrrolizidone (111).

The azetidinone structure (108) also agreed with the spectroscopic data available. It was thought to be one of the more likely possibilities since ring opening followed by ring closure to azetidinone structures had been noticed in the 5-unsubstituted isoxazolium salt series (See introduction p.32). Moll<sup>51</sup> had reported that 1-aza-bicyclo [4,2,0] octan-2-one (112) had an infrared carbonyl absorption at  $1756\text{ cm}^{-1}$  and work carried out on the penicillins<sup>52</sup> had given rise to many compounds with the general structure shown (113). These had a strong carbonyl absorption at  $1775\text{ cm}^{-1}$  which was close to the  $1778\text{ cm}^{-1}$  value obtained for the rearrangement product.



(112)



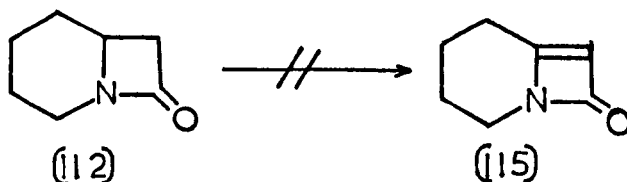
(113)

The azetidinone (112) was prepared<sup>53</sup> in the hope of introducing the required unsaturation to produce a model with which to compare the rearrangement product. Ethyl 2-pyridylacetate<sup>54</sup> was hydrogenated with Adams' catalyst in glacial acetic acid. Three molar equivalents of hydrogen were taken up to give a white deliquescent solid of unknown composition. This solid had also been obtained by Clemons, Morgan and Raper<sup>55</sup> in their original preparation of ethyl

2-piperidylacetate and had not been characterised. The reduction was repeated but the hydrogenation carried out under pressure ( $90 \text{ lb ins}^{-2}$ ), on distillation of the product the same deliquescent solid was obtained. The picrate derivative of this solid was purified by recrystallization. On dissolving this derivative in benzene and washing with 50% ammonium hydroxide solution a 50% recovery of pure ethyl 2-piperidylacetate (114) was obtained. The white solid could be converted into the ester directly in an 80% yield by dissolving it in chloroform and washing with ammonium hydroxide solution.

The ester (114) reacted with two equivalents of methyl magnesium iodide to give a tan coloured oil. This oil was extracted with toluene and washed with a saturated ammonium chloride solution. The product contained some unreacted amine which was eliminated by washing with a dilute hydrochloric acid solution. By addition of the Grignard reagent to the ester, a larger yield of the crude tan coloured oil was obtained but a decrease in the yield of purified azetidinone.

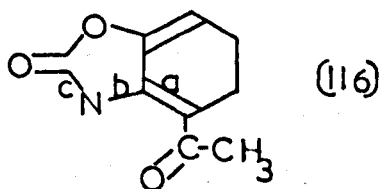
An attempt to dehydrogenate this azetidinone (112) by heating it under reflux in benzene in the presence of dichloro dicyano-1,4-benzoquinone failed.





Bromination of the azetidinone in the  $\alpha$ -position with N-bromosuccinimide followed by dehydrobromination to give the unsaturated product (115) also failed. Attempts to hydrogenate the azetidinone (112) with Adams' catalyst in ethanol were unsuccessful and the starting material was recovered unchanged, suggesting that if the rearrangement product had the structure (108) then hydrogenation could not proceed via the azetidinone (112).

An X-ray crystal study of the rearrangement product (109) from the isoxazolium salt (94) was carried out by Ferguson and Marsh.<sup>56</sup> They initially suggested the structure (116) which was not completely satisfactory in the degree of refinement. The structure was also chemically unsatisfactory since it was a dihydrobenzene and should have been readily dehydrogenated. Such a compound would also undergo Diels-Alder reactions.

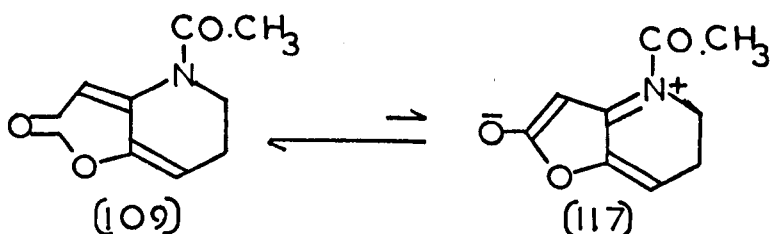


Because the bond lengths a, b and c were all between single and double C-C bond lengths some conjugation through these bonds was assumed. Exchanging C7 for N1 and rearranging these bonds gave a new structure (109) which agreed with all the chemical and spectroscopic evidence.

On re-examining their X-ray data in this light Ferguson

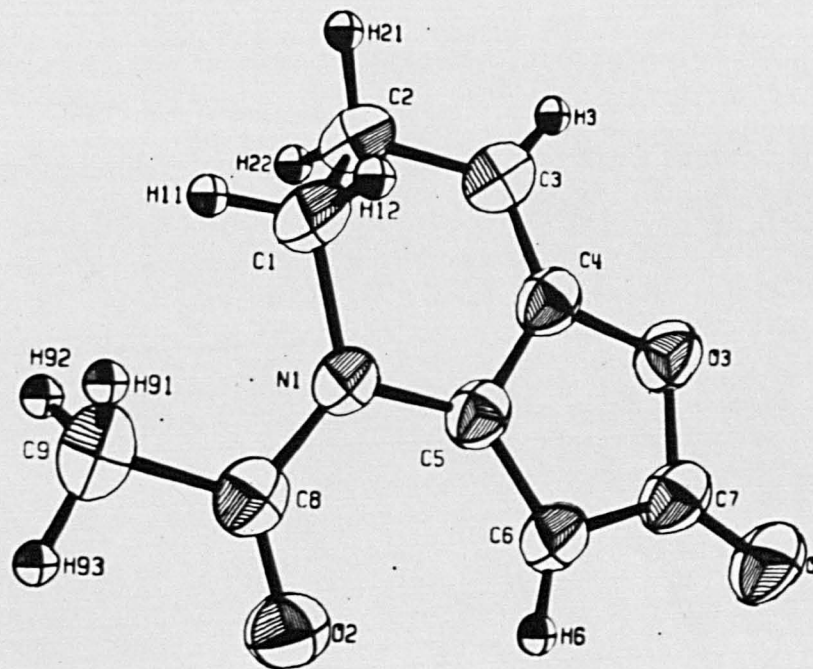
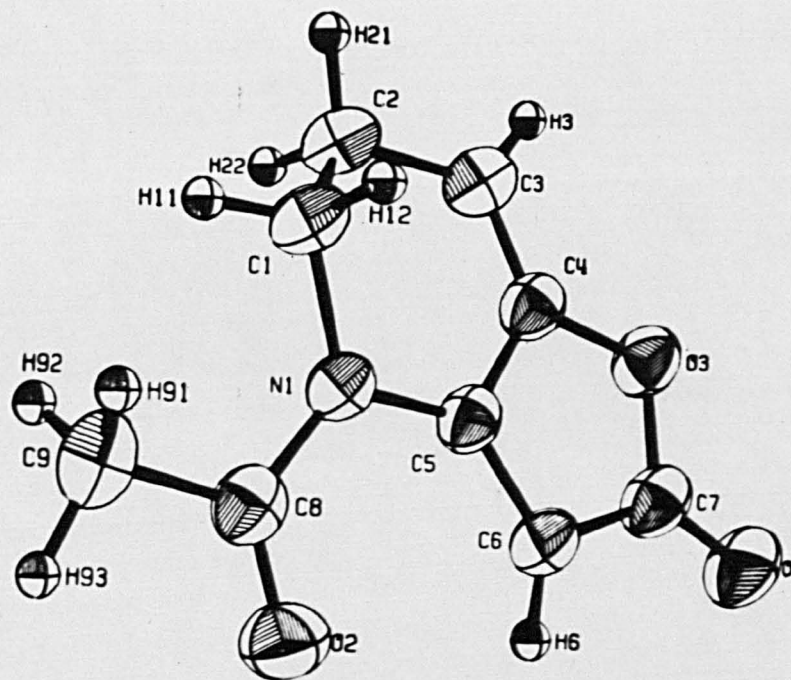
and Marsh found that a perfectly acceptable fit was obtained. A view of the molecule showing bond distances and the conformation is given on p.64.

The rearrangement product is a novel heterocyclic system which contains an enaminoketone backbone through atoms 2, 3, 3a and 4 and the possible conjugation is shown by the two forms (109) and (117).

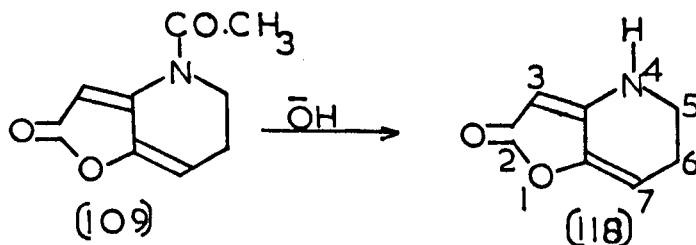


Hydrolysis of 4-acetyl-5,6-dihydro-4H-furo[3,2-b]pyrid-2-one (109) occurred very rapidly. This could be seen by the addition of a drop of dilute alkali solution to an ethanolic solution of the compound in an ultraviolet spectrometer cell. There was an irreversible change of the spectrum after this addition. The spectrum of the pyridone (109) consisted of an absorption at 276 nm. ( $\log_{10} \epsilon = 4.24$ ); on addition of the base this immediately changed to give two absorptions, at 260 nm. ( $\log_{10} \epsilon = 4.03$ ) and at the longer wavelength of 312 nm. ( $\log_{10} \epsilon = 3.82$ ). The longer wavelength absorption may have been due to the enaminoketone system since the nitrogen lone pair could be more readily incorporated into the chromophore. Prior to hydrolysis the lone pair was not so readily available being part of the N-acetyl amide system.

$C1 - C2 = 1.527,$      $C2 - C3 = 1.494,$      $C3 - C4 = 1.322,$      $C4 - C5 = 1.448,$      $C5 - N1 = 1.376,$   
 $N1 - C1 = 1.491,$      $C5 - C6 = 1.351,$      $C6 - C7 = 1.446,$      $C7 - O3 = 1.390,$      $C4 - O3 = 1.388,$   
 $C7 - O1 = 1.207,$      $N1 - C8 = 1.394,$      $C8 - C9 = 1.490,$      $C8 - O2 = 1.213.$



Preparations of the hydrolysis product (118) on a larger scale gave very variable yields since the product was heat sensitive. An almost quantitative yield could be realised if the solvent was kept to a minimum and the whole solution passed down a short alumina chromatography column.



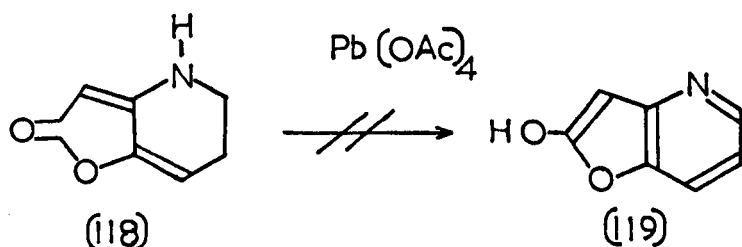
On removal of the acetyl group by hydrolysis the chemical shift of the olefinic proton H3 changed from  $\delta$  6.10 to 4.72 p.p.m. since the anisotropic deshielding effect of the proximal carbonyl group was removed. It was worth noting in the nuclear magnetic resonance spectrum the broad single proton absorption at  $\delta$  6.0 p.p.m. This disappeared on the addition of  $D_2O$  and was due to the amine proton. There was a single proton, split triplet absorption at  $\delta$  5.65 p.p.m. ( $J = 1\text{Hz}, 4\text{Hz}$ ) due to the olefinic proton H7 which was coupled to the other olefinic proton H3 and to the methylene protons at C6. These methylene protons at C6 appear as a multiplet at  $\delta$  2.45 p.p.m. The remaining signal at  $\delta$  3.4 p.p.m. was due to the methylene protons at C5 and appeared as a split triplet because they were coupled to the methylene protons at C7 and to the amine proton. This signal sharpened to a triplet on the addition of  $D_2O$  to the solution which

confirmed that it was coupled to the amine proton. This observation also indicated that the amine proton was exchanging relatively slowly. If the exchange was a rapid process then the methylene proton absorption would have appeared as a broadened signal rather than a sharply coupled one (N.M.R.p.67.)

A comparison of the chemical shift of the enaminoketone olefinic proton H3 and the ultraviolet absorption spectrum of the hydrolysed and unhydrolysed systems with other known enaminoketones is given in table 1. Some of the figures were provided by Dr. Hickmott of Salford University and the others are from work carried out by Cone, Garner and Hayes.<sup>57</sup>

The hydrolysis product (118) had a chemical shift for the olefinic proton H3 which was in good agreement with those of the five membered ring enaminoketones (iii) and (vii) and closely resembled all of the open chain examples (viii) to (xii).

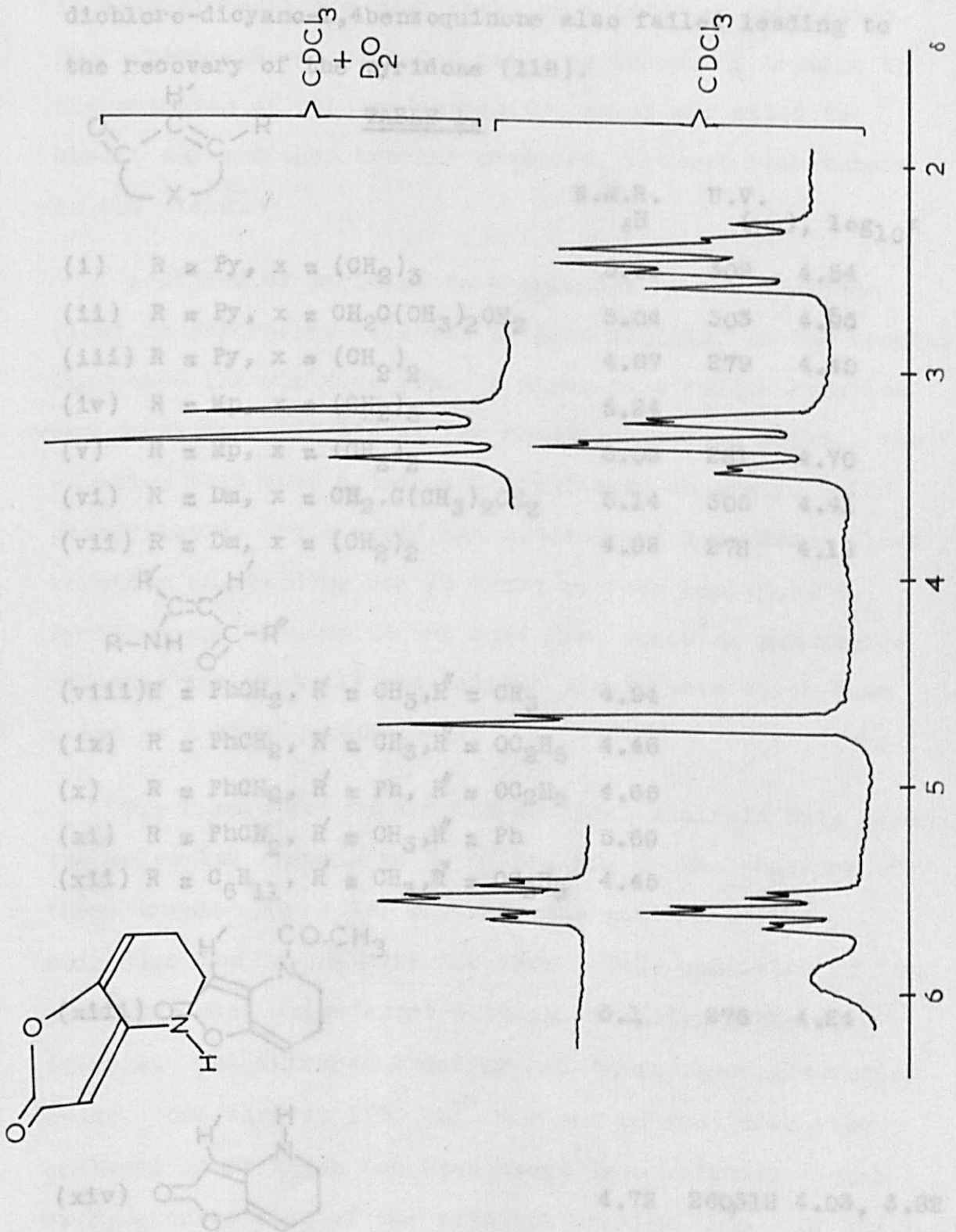
An attempt to oxidize the furopyridone (118) to the aromatic hydroxyfuropyridine (119) with lead tetraacetate gave only a polymeric residue.



N. m. r. Spectrum Of

5,6 - dihydro - 4H - furo [3,2-b] pyrid - 2 - one, with

dichloro-dicyano, benzenequinone also failed leading to the recovery of the pyridone (119).



Attempted dehydrogenation of the pyridone (118) with dichloro-dicyano-1,4benzoquinone also failed leading to the recovery of the pyridone (118).

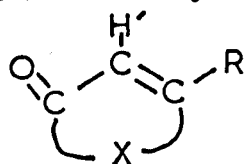
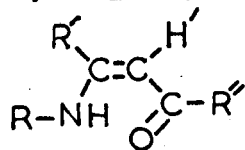
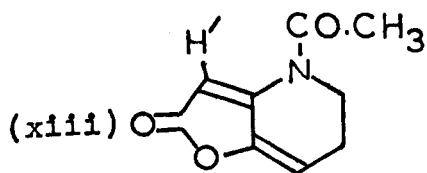


TABLE 1.

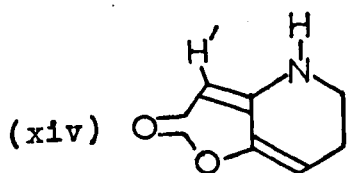
	N.M.R. $\delta H$	U.V. ( $m\mu$ ), $\log_{10} \epsilon$
(1) R = Py, x = (CH <sub>2</sub> ) <sub>3</sub>	5.06	302 4.54
(ii) R = Py, x = CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub>	5.04	303 4.53
(iii) R = Py, x = (CH <sub>2</sub> ) <sub>2</sub>	4.87	279 4.40
(iv) R = Mp, x = (CH <sub>2</sub> ) <sub>3</sub>	5.24	
(v) R = Mp, x = (CH <sub>2</sub> ) <sub>2</sub>	5.05	281 4.70
(vi) R = Dm, x = CH <sub>2</sub> .C(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub>	5.14	305 4.41
(vii) R = Dm, x = (CH <sub>2</sub> ) <sub>2</sub>	4.92	278 4.12



(viii) R = PhCH <sub>2</sub> , R' = CH <sub>3</sub> , R'' = CH <sub>3</sub>	4.94	
(ix) R = PhCH <sub>2</sub> , R' = CH <sub>3</sub> , R'' = OC <sub>2</sub> H <sub>5</sub>	4.46	
(x) R = PhCH <sub>2</sub> , R' = Ph, R'' = OC <sub>2</sub> H <sub>5</sub>	4.66	
(xi) R = PhCH <sub>2</sub> , R' = CH <sub>3</sub> , R'' = Ph	5.69	
(xii) R = C <sub>6</sub> H <sub>11</sub> , R' = CH <sub>3</sub> , R'' = OC <sub>2</sub> H <sub>5</sub>	4.45	



(xiii)	6.1	276 4.24
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(xiv)	4.72	260, 312 4.03, 3.82
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Py = pyrrolidino, Mp = morpholino, Dm = dimethylamino

Bromination of the furopyridone (109) with bromine in chloroform gave a poor yield of a tribromo derivative. The experiment was repeated using an excess of bromine in the presence of calcium carbonate, which was added to absorb any hydrogen bromide produced, without improvement in the yield.

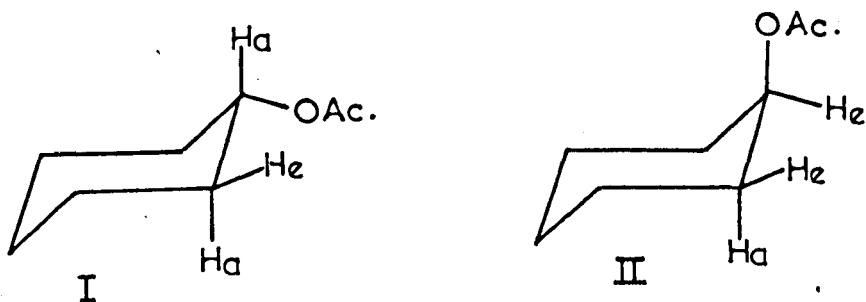
Addition of pyridine to a solution of the pyridone (109) in chloroform followed by slow addition of the bromine increased the yield to 20%. A clear pale yellow solution was obtained until 4/5 of the bromine had been added. The solution then went cloudy and eventually an orange solid precipitated. This solid had redissolved and gave a clear solution on standing for 16 hours at room temperature. Pyridine and bromine in the cold form pyridine perbromide and this was probably the initial precipitate which then acted as a brominating agent.

The mass spectrum and the chemical analysis have given the molecular formula as  $C_9 H_3 Br_3 NO_3$ . The presence of three bromine atoms was given by the pattern of the molecular ion in the mass spectrum. This consisted of four peaks two mass units apart with an intensity ratio of 1:3:3:1. The infrared spectrum had three major absorption bands. One band at  $1790\text{ cm}^{-1}$  was due to the furan ring carbonyl group which had been moved to a slightly higher wavenumber because of the adjacent bromine atom. Of the other two absorptions at  $1690$  and  $1640\text{ cm}^{-1}$ , the higher



wavenumber absorption was probably due to the N-acetyl amide carbonyl group and the lower one to the double bond stretching vibration.

The nuclear magnetic resonance spectrum (p.71) had no alkene proton absorptions. The signal at  $\delta$  4.95 p.p.m. was assigned to a methine group which bore a bromine atom. The low coupling constant of this signal ( $J \leq 3\text{Hz}$ ) suggested that this hydrogen was equatorial. This suggestion arose from a comparison with acetoxy cyclohexane:-



In structure I the acetoxy group was equatorial and the proton attached to the same carbon was therefore axial. This axial proton coupled to the adjacent methylene hydrogens with a different coupling constant according to which of them was considered (because of the difference in dihedral angle)  $J_{aa} = 11.4\text{Hz}$ ,  $J_{ae} = 4.2\text{Hz}$ . From this the spectral pattern that would be expected could be deduced.

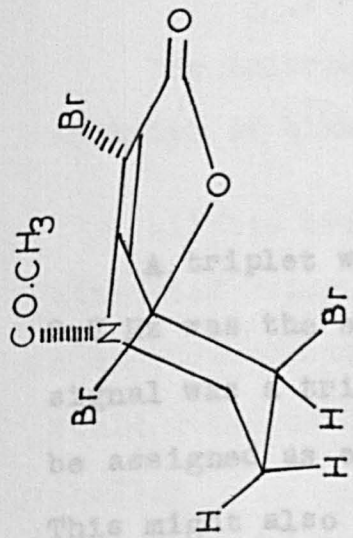
N.m.r. Spectrum Of  
tri-bromofuropyridone.

$\leftarrow 4.2\text{Hz} \rightarrow$

$\leftarrow 4.2\text{Hz} \rightarrow$

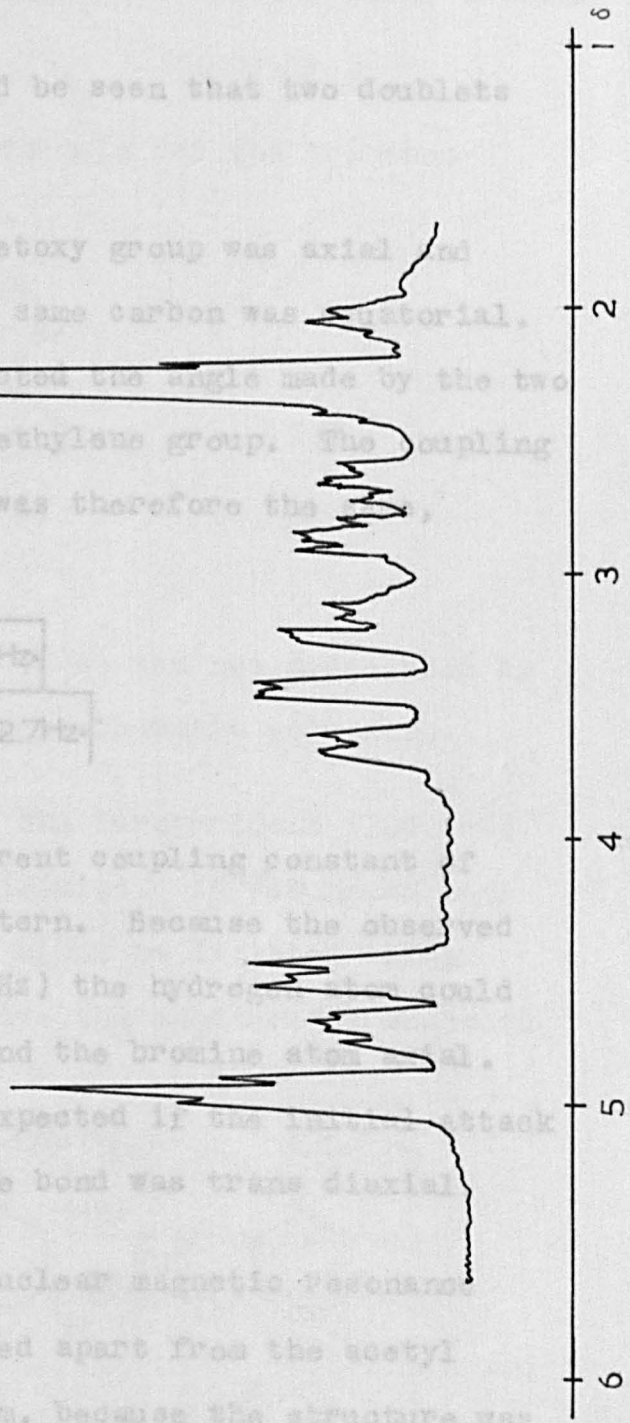
From the above it could be seen that two doublets would be expected.

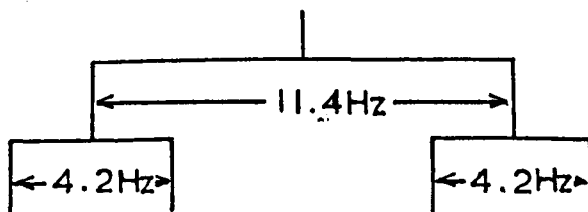
In structure II the acetoxy group was axial and therefore the proton on the same carbon was equatorial. The coupling constants to each of these was therefore the same,  $J_{\text{ax-eq}} = J_{\text{eq-eq}} = 2.7 \text{ Hz}$ .



$\leftarrow 2.7\text{Hz} \rightarrow$   
 $\leftarrow 2.7\text{Hz} \rightarrow$

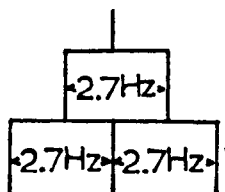
The remainder of the nuclear magnetic resonance spectrum was very complicated apart from the acetyl methyl signal at  $\delta 2.3 \text{ p.p.m.}$  Because the structure was conformationally tied. There was a single proton





From the above it could be seen that two doublets would be expected.

In structure II the acetoxy group was axial and therefore the proton on the same carbon was equatorial. This equatorial proton bisected the angle made by the two hydrogens on the adjacent methylene group. The coupling constants to each of these was therefore the same,  $J_{ea} = J_{ee} = 2.7 \text{ Hz}$ .

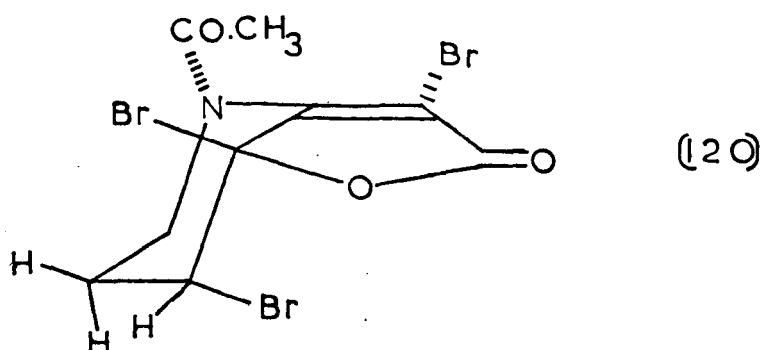


A triplet with an apparent coupling constant of 2.7 Hz was the expected pattern. Because the observed signal was a triplet ( $J \leq 3\text{Hz}$ ) the hydrogen atom could be assigned as equatorial and the bromine atom axial. This might also have been expected if the initial attack of the bromine on the double bond was trans diaxial.

The remainder of the nuclear magnetic resonance spectrum was very complicated apart from the acetyl methyl signal at  $\delta 2.3 \text{ p.p.m.}$  because the structure was conformationally tied. There was a single proton

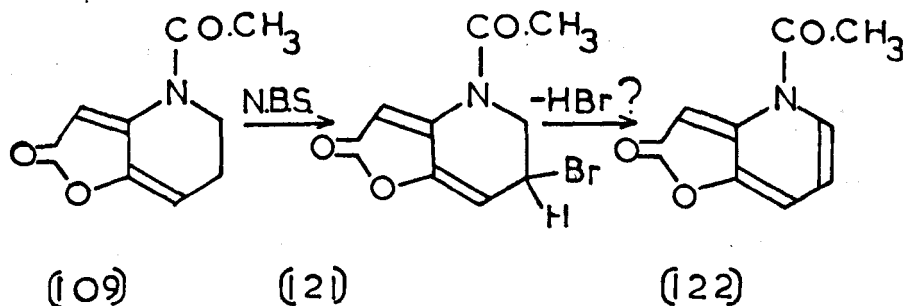
multiplet centered at  $\delta$  4.65 p.p.m. which may have been due to the axial proton of the methylene group at C5. This appeared downfield in comparison with the rest because of the 1,3-deshielding effect of the axial bromine atom.

The most satisfactory formula for the tribromo-furopyridone (120) is shown.

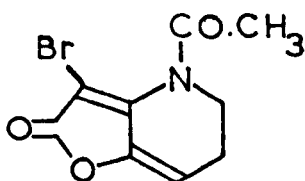


The tribromoderivative (120) was not hydrolysed by addition of alkali to a dilute ethanolic solution.

Allylic bromination of the furopyridone (109) was attempted using N-bromosuccinimide. It was hoped that a monobromoderivative (121) might be isolated which would dehydrobrominate to give the unsaturated compound (122).



Heating the furopyridone (109) under reflux in chloroform with N-bromosuccinimide and concomitant irradiation led to the isolation of a very small amount of material. The structure was decided by nuclear magnetic resonance spectroscopy (p.75) to be the monobromoderivative (123).



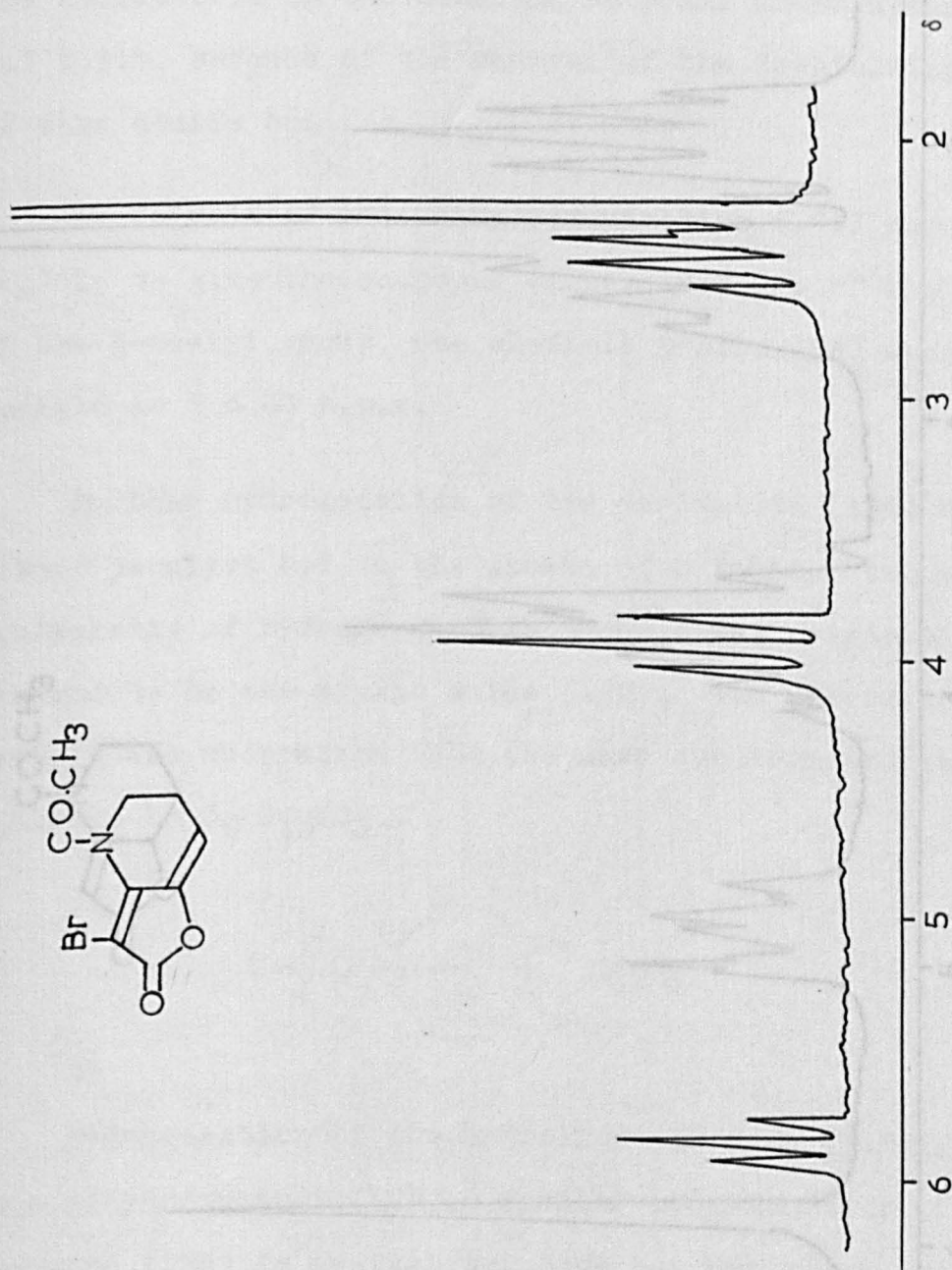
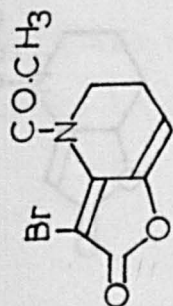
(123)

It appeared that the bromine had substituted at C3 because the signal at  $\delta$  6.1 p.p.m. disappeared and the split triplet at  $\delta$  5.8 p.p.m. (H7) collapsed to a triplet. Repeating this experiment under different reaction conditions led to no isolated products.

Hydrogenation of the furopyridone (109) using a 10% palladium on charcoal catalyst led to the uptake of one molar equivalent of hydrogen to give a dihydroderivative<sup>58</sup> (124). The mass spectrum and chemical analysis gave the formula as  $C_9H_{11}NO_3$ . The nuclear magnetic resonance spectrum (p.76) had a sharp singlet at  $\delta$  5.9 p.p.m. due to H3 and a multiplet at  $\delta$  4.85 p.p.m. due to the proton H7a.

N.m.r. Spectrum Of

4-Acetyl-3-bromo-5,6-dihydro-4H-furo [3,2-b] pyrid-2-one.



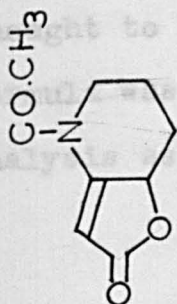
The N.m.r. Spectrum Of  
4-Acetyl-5,6,7,7a-tetrahydro-4H-furo[3,2-b]pyrid-2-one

signal due to the methylene group (18) which was assigned to the double bond in the starting material was assigned by 0.7 p.p.m. because of the removal of the olefinic effect of this double bond.

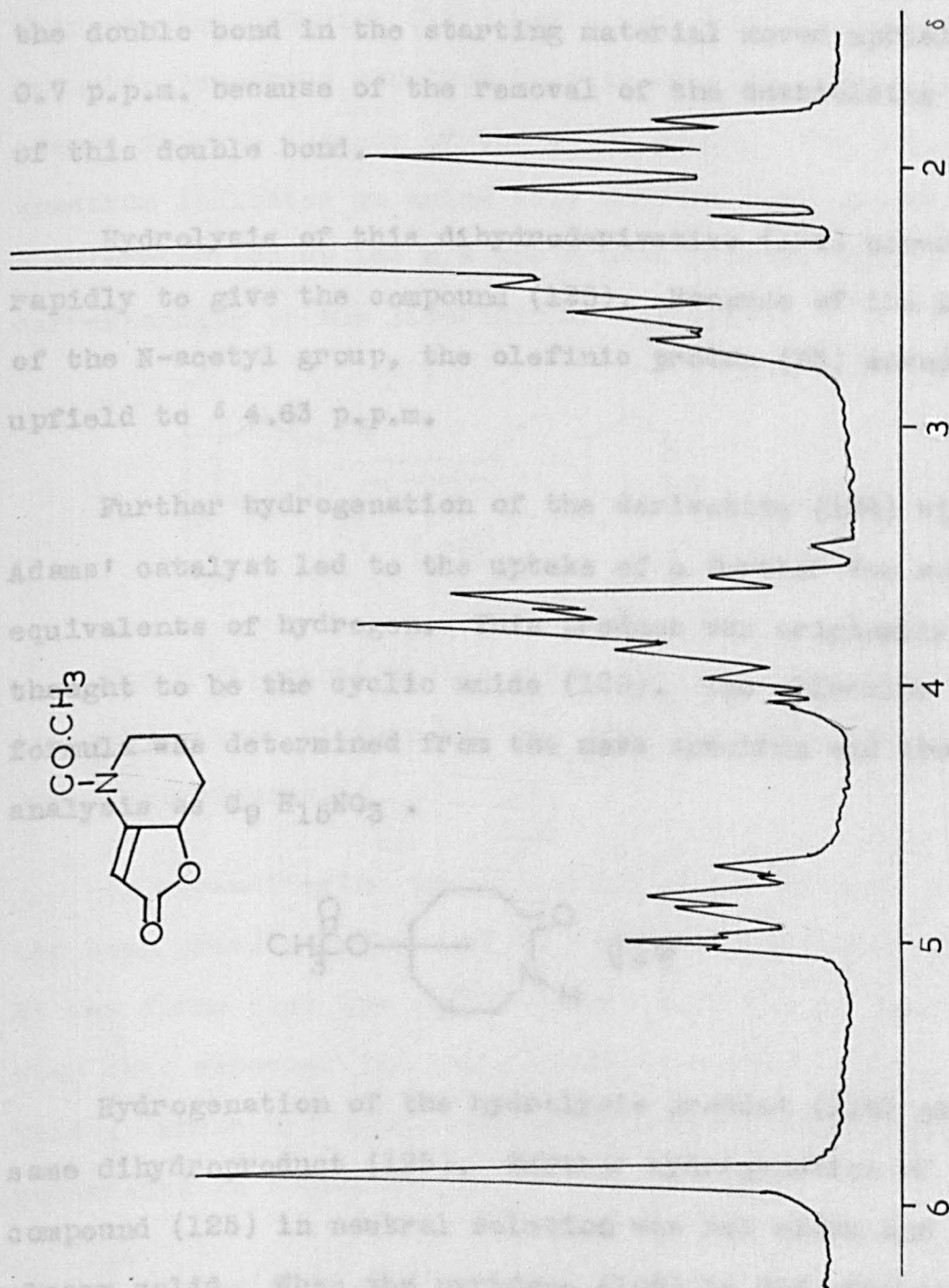
Hydrolysis of this dihydrofuran derivative rapidly to give the compound (125) because of the presence of the N-acetyl group, the olefinic protons were shifted upfield to  $\delta$  4.63 p.p.m.

Further hydrogenation of the derivative (125) with Adams' catalyst led to the uptake of 2 equivalents of hydrogen to give the compound (126) which was thought to be the cyclic amide (126).

For the determination of the structure of the compound (126) the mass spectrum was determined and the molecular ion was found to be  $C_{10}H_{16}NO_3$ .



Hydrogenation of the hydrolysis product (125) with Adams' catalyst led to the uptake of 2 equivalents of hydrogen to give the compound (126) in neutral solution. The compound (126) was a glassy solid. When the pyridine ring of the compound was treated with sodium hydride in dry THF, the compound was converted to a solution hydrogenated a very much slower rate.

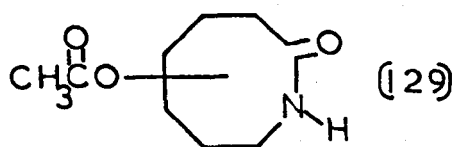




The three methylene absorptions were at  $\delta$  1.93 (H6), 2.5 (H7) and 3.8 (H5) p.p.m. It could be seen that the signal due to the methylene group (H6) which was next to the double bond in the starting material moved upfield by 0.7 p.p.m. because of the removal of the deshielding effect of this double bond.

Hydrolysis of this dihydroderivative (124) occurred rapidly to give the compound (125). Because of the loss of the N-acetyl group, the olefinic proton (H3) moved upfield to  $\delta$  4.63 p.p.m.

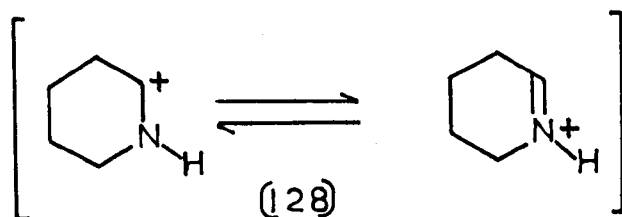
Further hydrogenation of the derivative (124) with Adams' catalyst led to the uptake of a further two molar equivalents of hydrogen. This product was originally thought to be the cyclic amide (129). The molecular formula was determined from the mass spectrum and chemical analysis as  $C_9H_{15}NO_3$ .



Hydrogenation of the hydrolysis product (118) gave the same dihydroproduct (125). Further hydrogenation of this compound (125) in neutral solution was not clean and gave a glassy solid. When the pyridone (109) in 95% ethanol was treated with sodium hydroxide solution and this alkaline solution hydrogenated a very much cleaner reaction occurred.



A white crystalline solid identified as the salt (127) was isolated. The same material was obtained by hydrogenating the dihydropyridone (125) in an alkaline medium. The fully hydrogenated material (127) had a very similar nuclear magnetic resonance spectrum to that of ethyl piperidylacetate except for the absence of the ester group. The infrared spectrum indicated an amino acid and the mass spectrum gave a molecular ion at 143 m/e and a base peak at 84 m/e corresponding to the piperidinium ion (128).



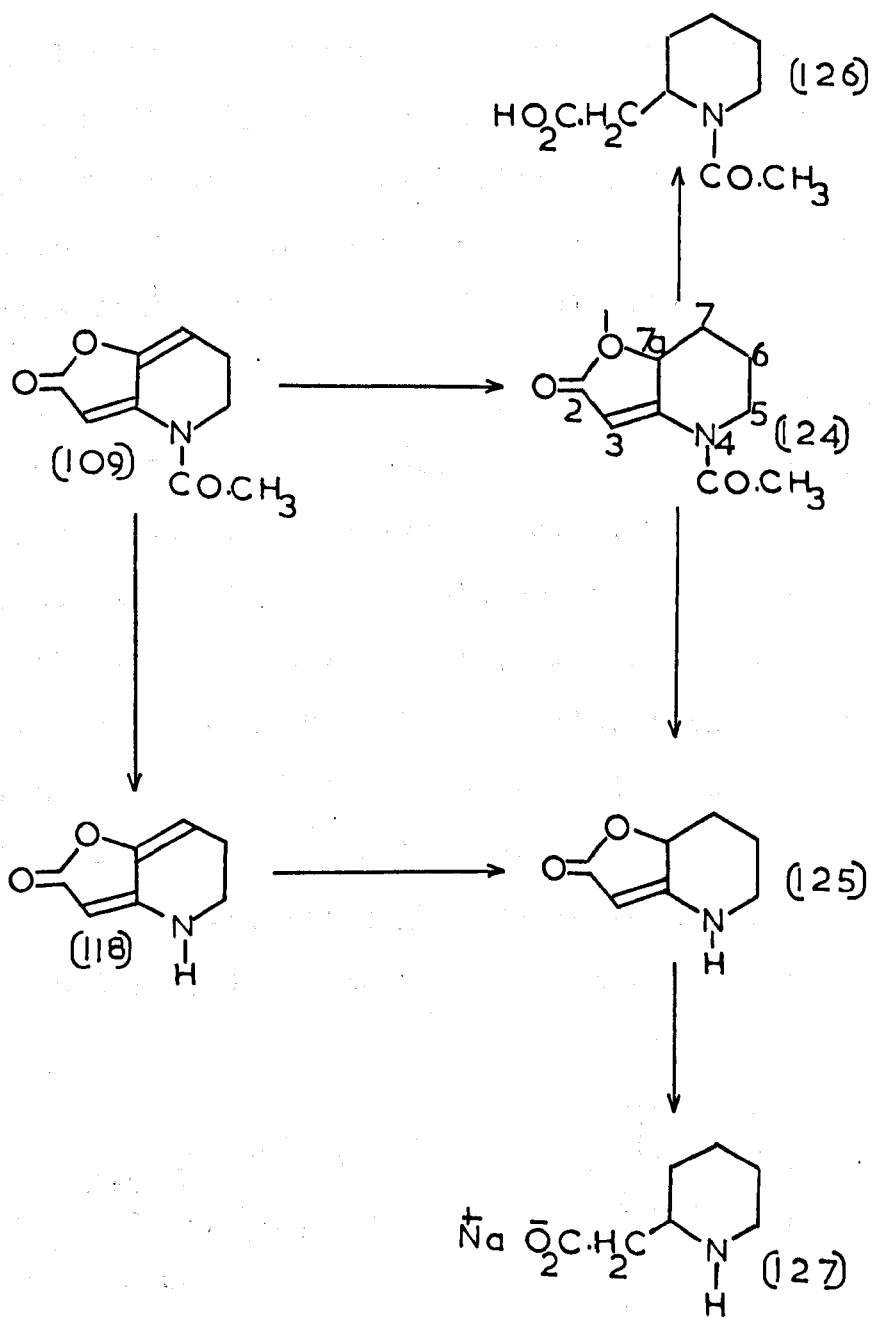
The 2-piperidyl acetic acid (127) was characterised as its ethyl ester picrate and was identical to a sample prepared unambiguously.

On reconsidering the structure of the product which had been previously assumed to be the cyclic amide (129) it was found that the spectroscopic data was in agreement with that expected for N-acetyl-2-piperidyl acetic acid (126). These hydrogenation and hydrolysis experiments are summarised in scheme 22.

#### (iii) Mechanisms for the rearrangement.

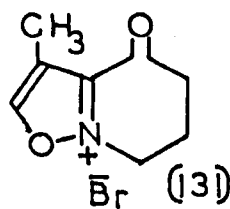
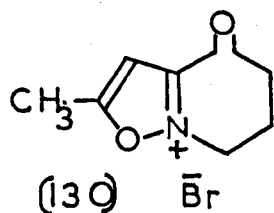
The mechanism of the rearrangement of the bicyclic salt (94) to the furopyridone (109) was thought to proceed

# Scheme 22



via the loss of the proton at position 2. Proof that this proton was directly involved in the rearrangement was obtained by treating the two salts (130) and (131) with acetic anhydride. These two salts were prepared by an analogous route to that used for salt (94).

Isopropenyl acetate and triethylamine in ether were heated under reflux whilst an ethereal solution of carbethoxy-chloraldoxime was added. The crude product was heated to eliminate acetic acid and the resultant 3-carbethoxy-5-methylisoxazole (132) was distilled. The ester (132) was converted to the amide with ammonia solution and then dehydrated to the nitrile (133). This nitrile (133) condensed with 3-ethoxypropyl magnesium bromide to give 3-(4-ethoxybutyryl)-5-methylisoxazole (134) which readily cyclised in hydrobromic acid to the salt (130).



From this salt (130) no product was isolated after heating with acetic anhydride.

Methyl crotonate was prepared by a general procedure described by Bedouakin<sup>62</sup> and dissolved in ether containing triethylamine. To the boiling solution was added an ethereal solution of carbethoxy-chloraldoxime. The

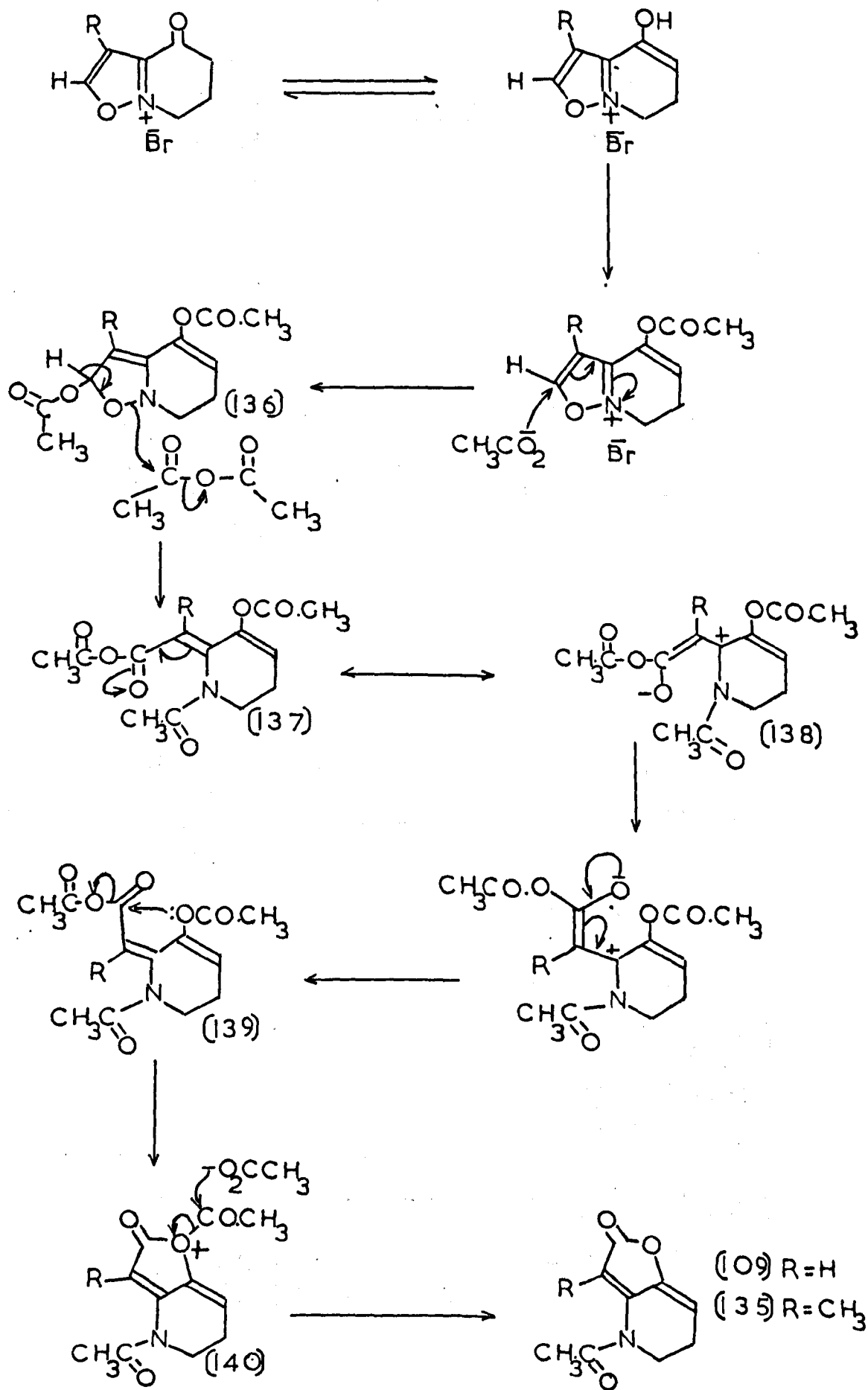
3-carbethoxy-4-methylisoxazole obtained after the elimination of acetic acid proved more difficult to convert into the amide than the other esters. The yield of amide from aqueous ammonia was 20%, improved to 50% by saturating a methanolic solution of the ester with ammonia gas. The amide was dehydrated to the nitrile, condensed with 3-ethoxypropyl magnesium bromide and the resultant ether cyclised in hydrobromic acid to give the salt (131).

This cyclic salt (131) readily underwent rearrangement with acetic anhydride to give 4-acetyl-5,6-dihydro-3-methylfuro [3,2-b] pyrid-2-one (135).

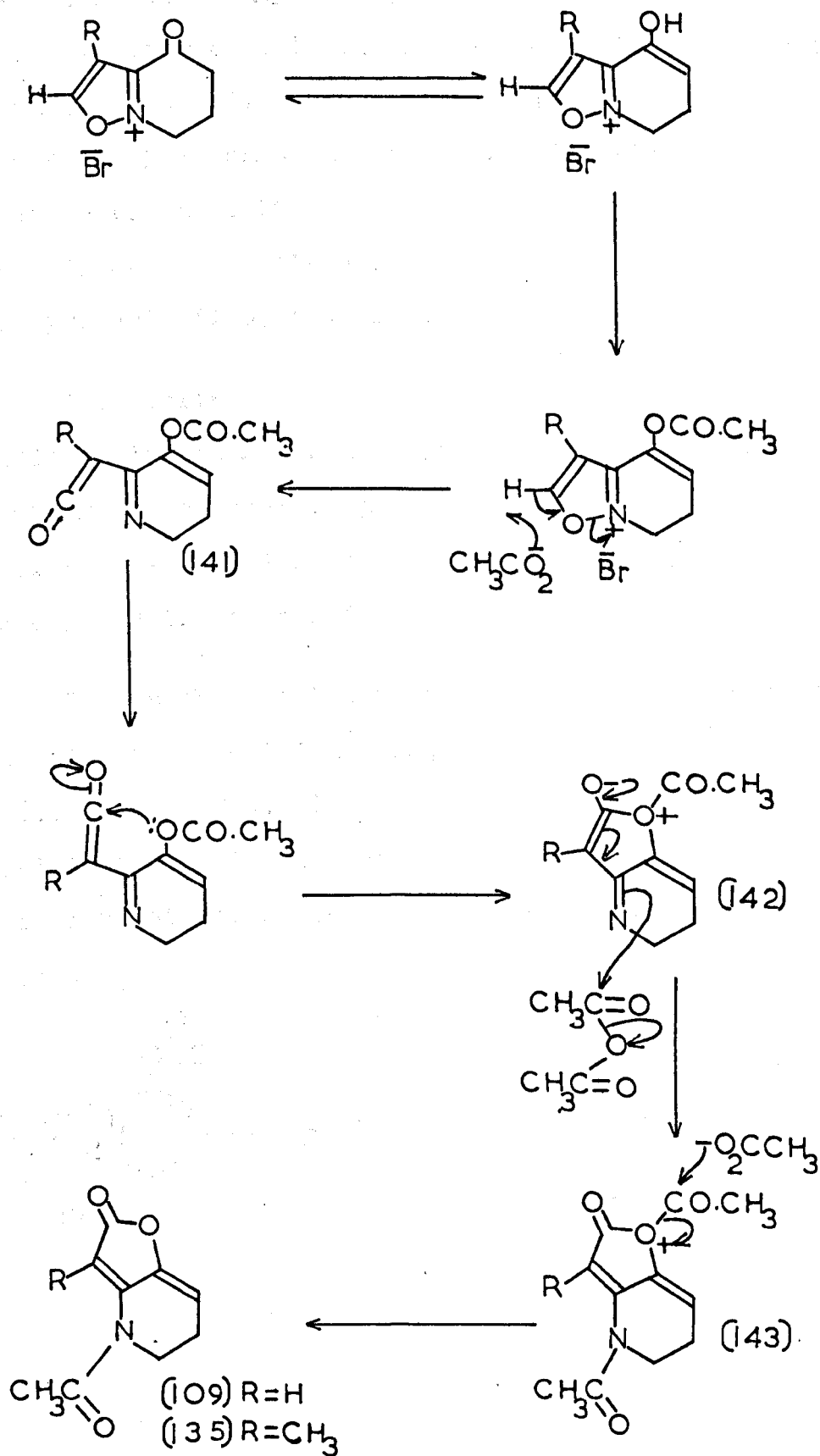
From these experiments it could be deduced that the proton at position 2 of the salts (94) and (131) were involved in some way in the mechanism of the rearrangement.

There were two possible mechanisms which could be postulated involving the proton at position 2. and which resulted in the products described. In both of these (schemes 23 and 24) the initial step was assumed to be enolisation followed by enolacetate production. This was similar to the first steps in the aromatization reaction mechanism in the production of the quinolizinium salts (see scheme 20). Here the two mechanisms took different routes, the acetate anion present in small proportions in acetic anhydride added to position 2 of the cyclic salt and gave an uncharged intermediate (136). This isoxazoline (136) could have lost the proton from position 2 with

# Scheme 23



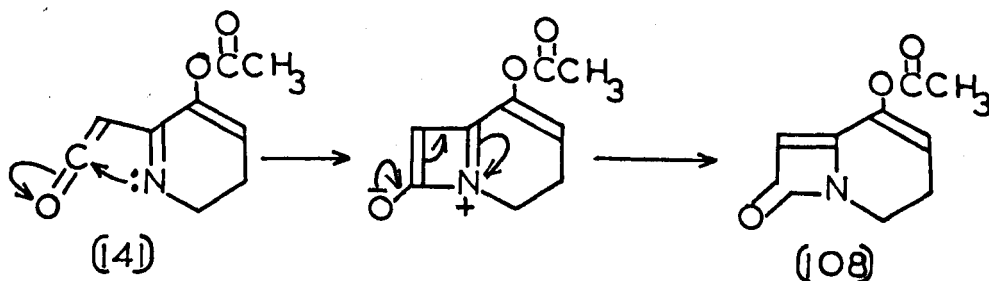
Scheme 24



attack on one acetyl group of acetic anhydride to give the N-acetyl mixed anhydride (137). It was possible to assume isomerisation of this anhydride (137) via the canonical form (138) to give the anhydride (139). Attack of the enol acetate oxygen onto the anhydride with elimination of the acetate anion would give the charged intermediate (140). This intermediate (140) could lose the acetyl group to give the products (109) and (135).

Isoxazolines have been shown to be possible intermediates in the rearrangements of isoxazolium salts (p.29). However these suggestions do not appear to have been as well substantiated as the proton abstraction mechanism more generally favoured.

Proton abstraction by the acetate nucleophile in solution from position 2 led to the ketene intermediate (141) (scheme 24). It was at this stage that it had been anticipated that the azetidinone structure (108) may have arisen by attack of the nitrogen lone pair on the ketene group.



It is possible to envisage rotation about the C-C single bond as shown and attack of the enol acetate oxygen lone pair on the ketene group to give the furan intermediate (142). Bond reorganisation, attack on one acetyl group of acetic anhydride would give the intermediate (143). This intermediate can lose the O-acetyl group to give the products (109) and (135).

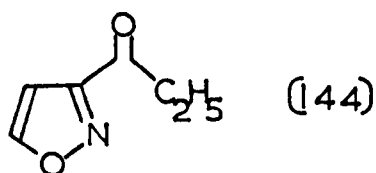
An attempt was made to see if the enolisation step was essential in the rearrangement process. Reduction of the carbonyl group of the cyclic ketone (94) would ensure that no enolisation could take place. Reduction with sodium borohydride in ethanol gave no product containing isoxazole proton absorptions in the nuclear magnetic resonance spectrum. It was assumed that because the reaction medium was slightly alkaline, ring opening had occurred (see p.88) to give the intractable polymeric product obtained.

Reduction of ethoxybutyryl isoxazole (99) with sodium borohydride gave 3-(4-ethoxy-3-hydroxybutyl) isoxazole. Heating this material in hydrobromic acid gave an hygroscopic solid which did not rearrange with acetic anhydride. This solid may have been 3-(4-bromo-1-hydroxybutyl) isoxazole hydrobromide but neutralisation with aqueous sodium bicarbonate solution and extraction with chloroform gave a negligible amount of material.

A simple model was prepared by treating



3-cyanoisoxazole with ethyl magnesium iodide to give the ketone (144). Quaternisation of this ketone (144) proved impossible with benzyl bromide in sulpholane and heating it in a sealed tube with methyl iodide gave only a carbonaceous mass. It appeared that quaternisation of 3-acylisoxazoles was difficult probably because the isoxazole nitrogen loses even its slightly basic properties because of the electron withdrawing effect of the carbonyl group.



By treating the ketone (144) with concentrated sulphuric acid it was hoped that the nitrogen would be protonated. This acidic mixture was then heated in acetic anhydride. From the nuclear magnetic resonance spectrum of the products it was concluded that a mixture of the starting material and the enolacetate was obtained. The shaded parts of the spectrum on p.87 were assigned to the ketone (144) and the remainder to its enolacetate derivative.

Other methods of influencing the enolic properties of the carbonyl group at position 4 of salt (94) were to attach a substituent  $\alpha$  to it or to make it part of a seven membered ring. Treatment of the ether (99) with sodium hydride and benzyl bromide gave no C-alkylated products. From 3-cyanoisoxazole and 4-ethoxybutyl magnesium bromide, 3-(5-ethoxyvaleryl) isoxazole was prepared. This also

N.M.R. Spectrum Of The

Isoxazole (144) And Its Enolacetate Derivative

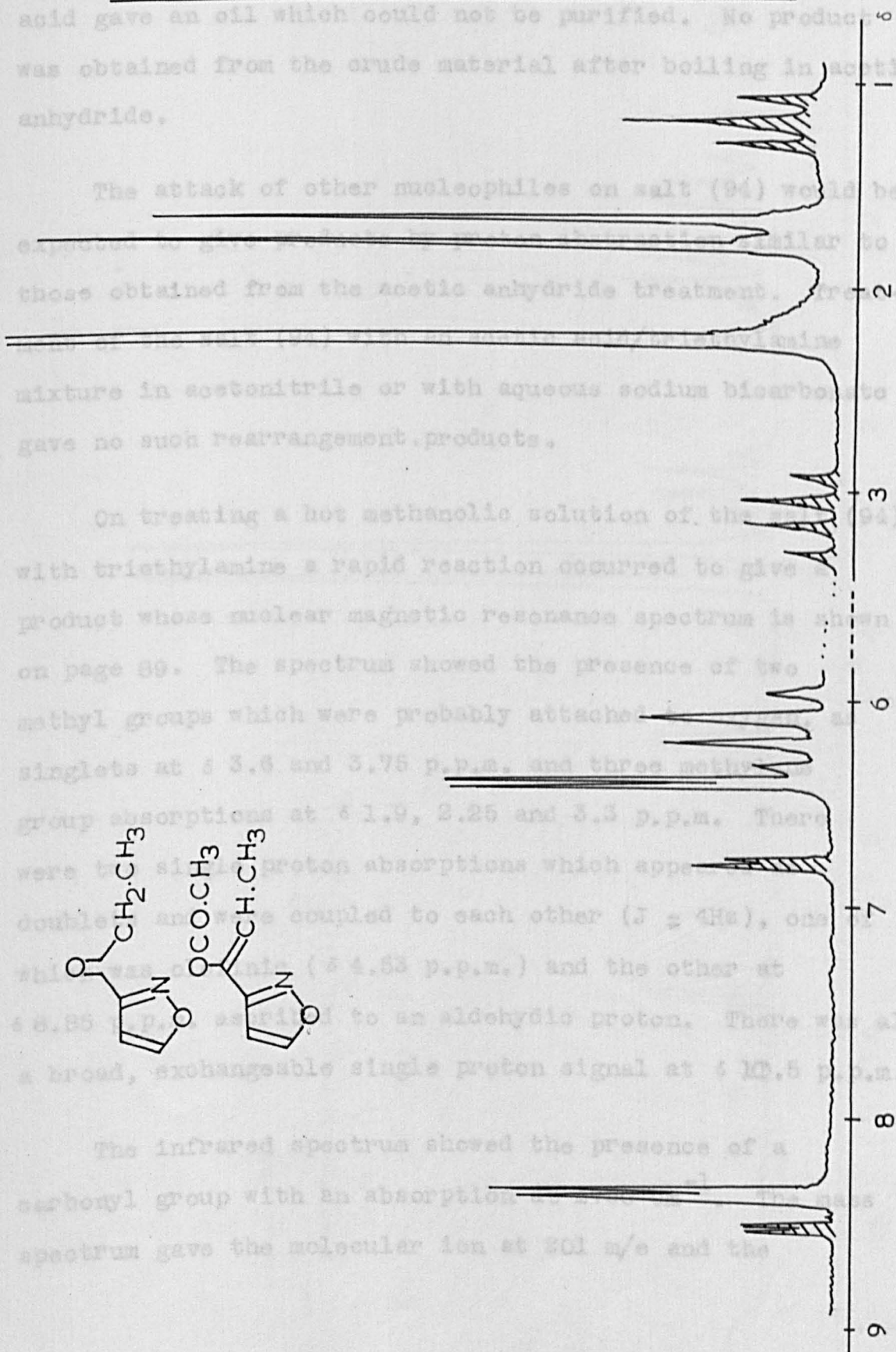
proved difficult to crystallize. Hydrobromic acid gave an oil which could not be purified. No product was obtained from the crude material after boiling in acetic anhydride.

The attack of other nucleophiles on salt (94) would be expected to give products similar to those obtained from the acetic anhydride treatment. A mixture in acetonitrile or with aqueous sodium bicarbonate gave no such rearrangement products.

On treating a hot methanolic solution of the (94) with triethylamine a rapid reaction occurred to give a product whose nuclear magnetic resonance spectrum is shown on page 89. The spectrum showed the presence of two methyl groups which were probably attached to the

singlets at  $\delta$  3.6 and 3.76 p.p.m. and three methoxy group absorptions at  $\delta$  1.9, 2.25 and 3.3 p.p.m. There were two olefinic proton absorptions which appeared as doublets and were coupled to each other ( $J = 4\text{ Hz}$ ), one at  $\delta$  4.83 p.p.m. and the other at  $\delta$  5.85 p.p.m. assigned to an aldehydic proton. There was also a broad, exchangeable single proton signal at  $\delta$  10.5 p.p.m.

The infrared spectrum showed the presence of a carbonyl group with an absorption at  $1710\text{ cm}^{-1}$ . The mass spectrum gave the molecular ion at 201 m/e and the



proved difficult to quaternise; cyclisation in hydrobromic acid gave an oil which could not be purified. No product was obtained from the crude material after boiling in acetic anhydride.

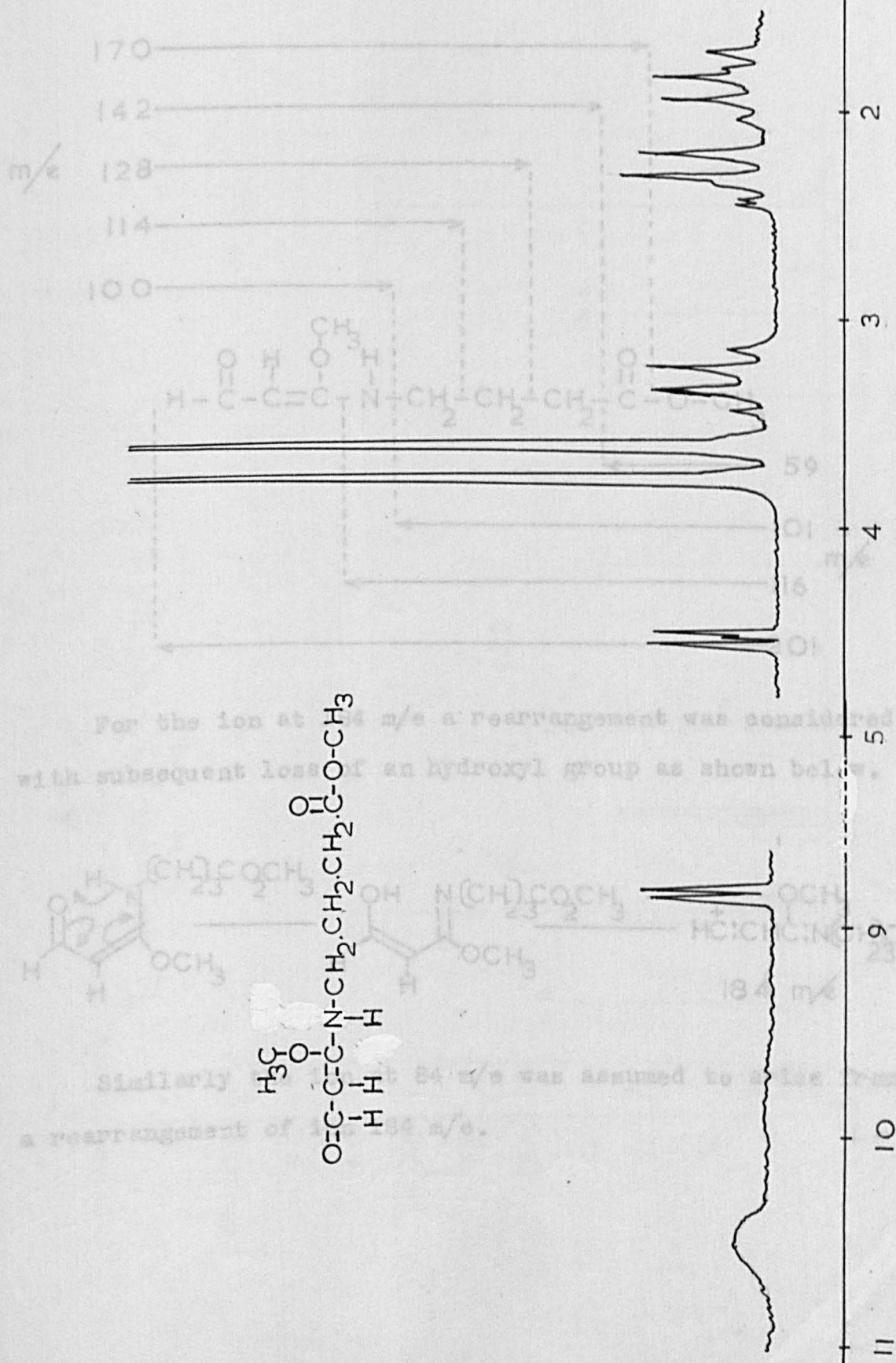
The attack of other nucleophiles on salt (94) would be expected to give products by proton abstraction similar to those obtained from the acetic anhydride treatment. Treatment of the salt (94) with an acetic acid/triethylamine mixture in acetonitrile or with aqueous sodium bicarbonate gave no such rearrangement products.

On treating a hot methanolic solution of the salt (94) with triethylamine a rapid reaction occurred to give a product whose nuclear magnetic resonance spectrum is shown on page 89. The spectrum showed the presence of two methyl groups which were probably attached to oxygen, as singlets at  $\delta$  3.6 and 3.75 p.p.m. and three methylene group absorptions at  $\delta$  1.9, 2.25 and 3.3 p.p.m. There were two single proton absorptions which appeared as doublets and were coupled to each other ( $J = 4\text{Hz}$ ), one of which was olefinic ( $\delta$  4.53 p.p.m.) and the other at  $\delta$  8.85 p.p.m. ascribed to an aldehydic proton. There was also a broad, exchangeable single proton signal at  $\delta$  10.5 p.p.m.

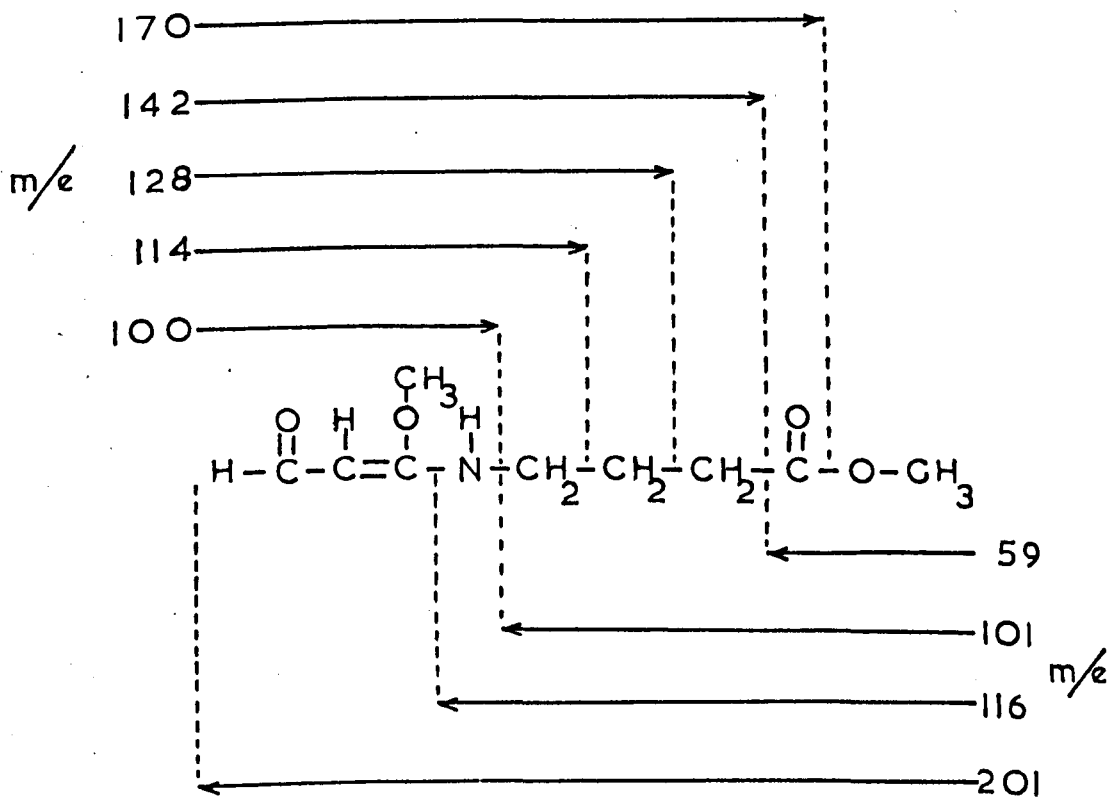
The infrared spectrum showed the presence of a carbonyl group with an absorption at  $1730\text{ cm}^{-1}$ . The mass spectrum gave the molecular ion at  $201\text{ m/e}$  and the

N. m. r. Spectrum Of The  
Vinylogous Amide (145)

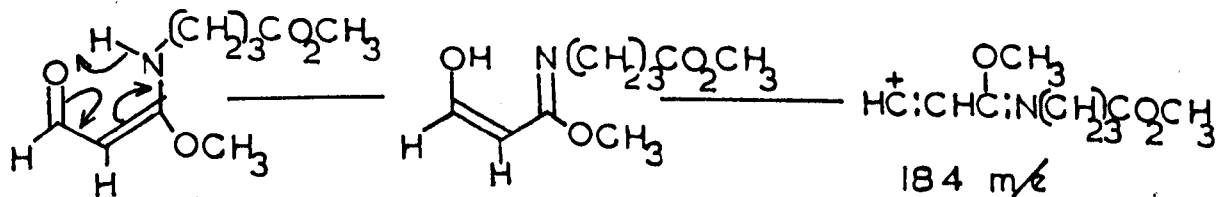
breakdown pattern given on page 91. Most of the peaks were assigned by assuming that the aldehyde (145) broke down into a group at a time as shown.



breakdown pattern given on page 91. Most of the peaks were assigned by assuming that the aldehyde (145) broke down a group at a time as shown.

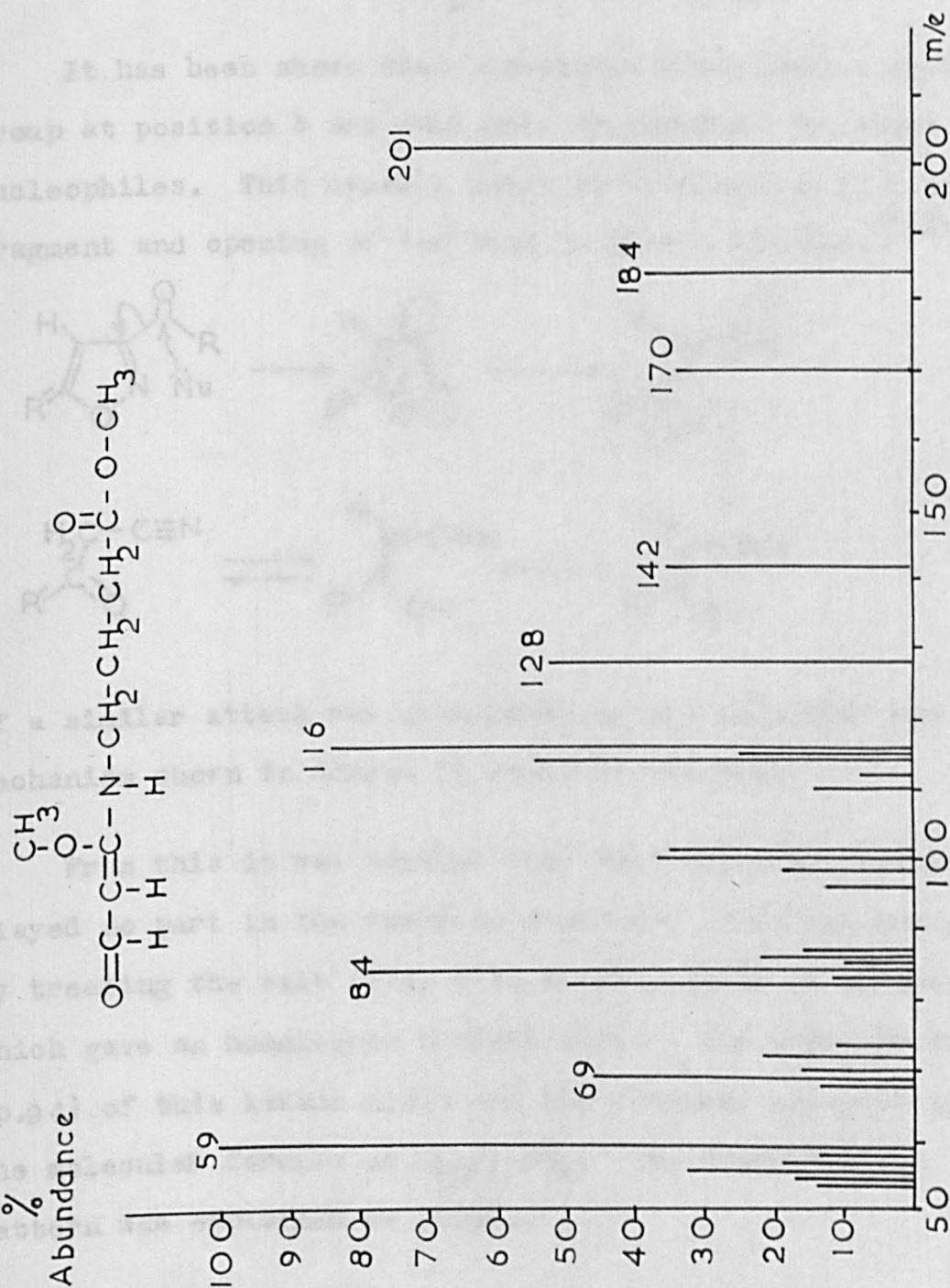
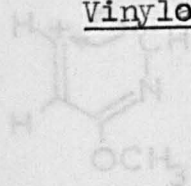


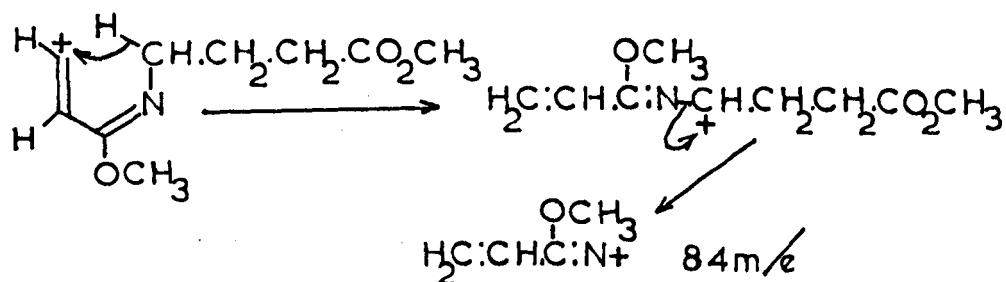
For the ion at 184  $m/e$  a rearrangement was considered with subsequent loss of a hydroxyl group as shown below.



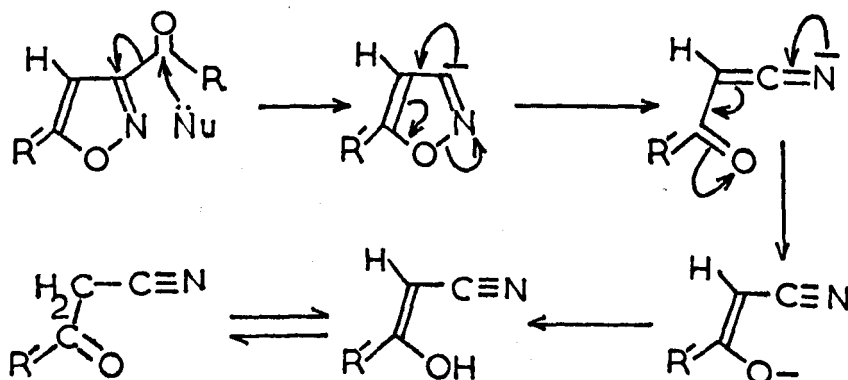
Similarly the ion at 84  $m/e$  was assumed to arise from a rearrangement of ion 184  $m/e$ .

Mass Spectrum Of The  
Vinylogous Amide (145).





It has been shown that isoxazoles which have a carbonyl group at position 3 are much more susceptible to attack by nucleophiles. This usually leads to elimination of a ketone fragment and opening of the ring to give a nitrile.<sup>59,60</sup>

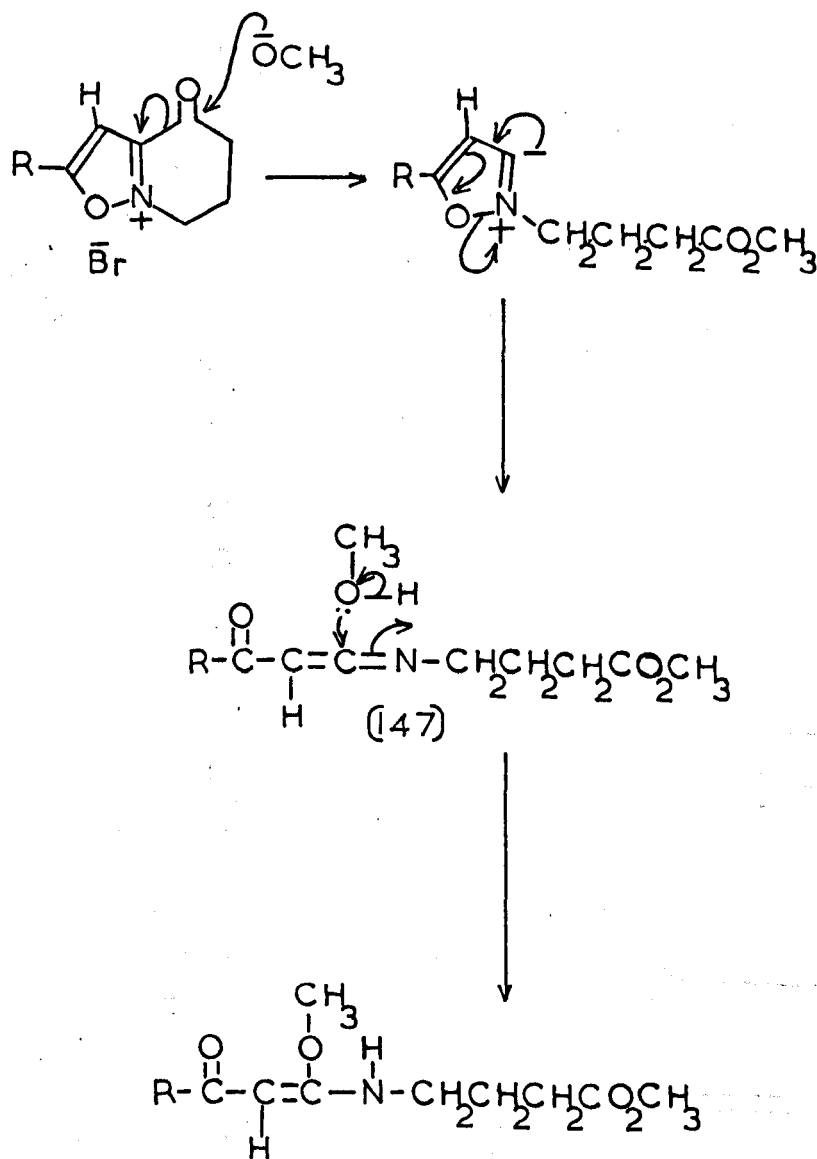


If a similar attack was postulated on the salt (94) the mechanism shown in scheme 25 would be expected.

From this it was assumed that the proton at position 2 played no part in the reaction sequence. This was supported by treating the salt (130) with triethylamine in methanol which gave an homologous product (146). The mass spectrum (p.94) of this ketone (146) and the chemical analysis gave the molecular formula as  $C_{10}H_{17}NO_4$ . The fragmentation pattern was explained as shown.

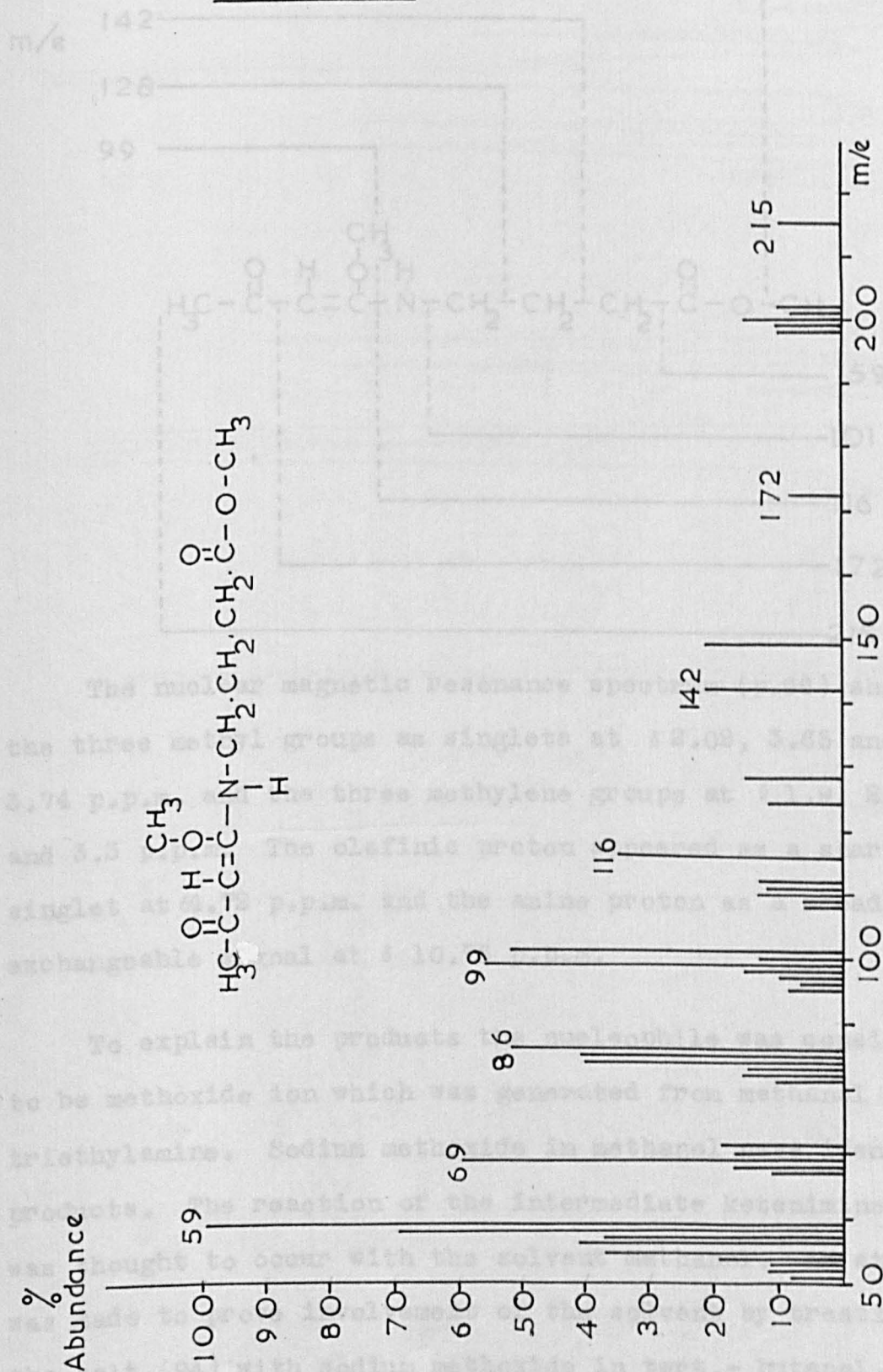


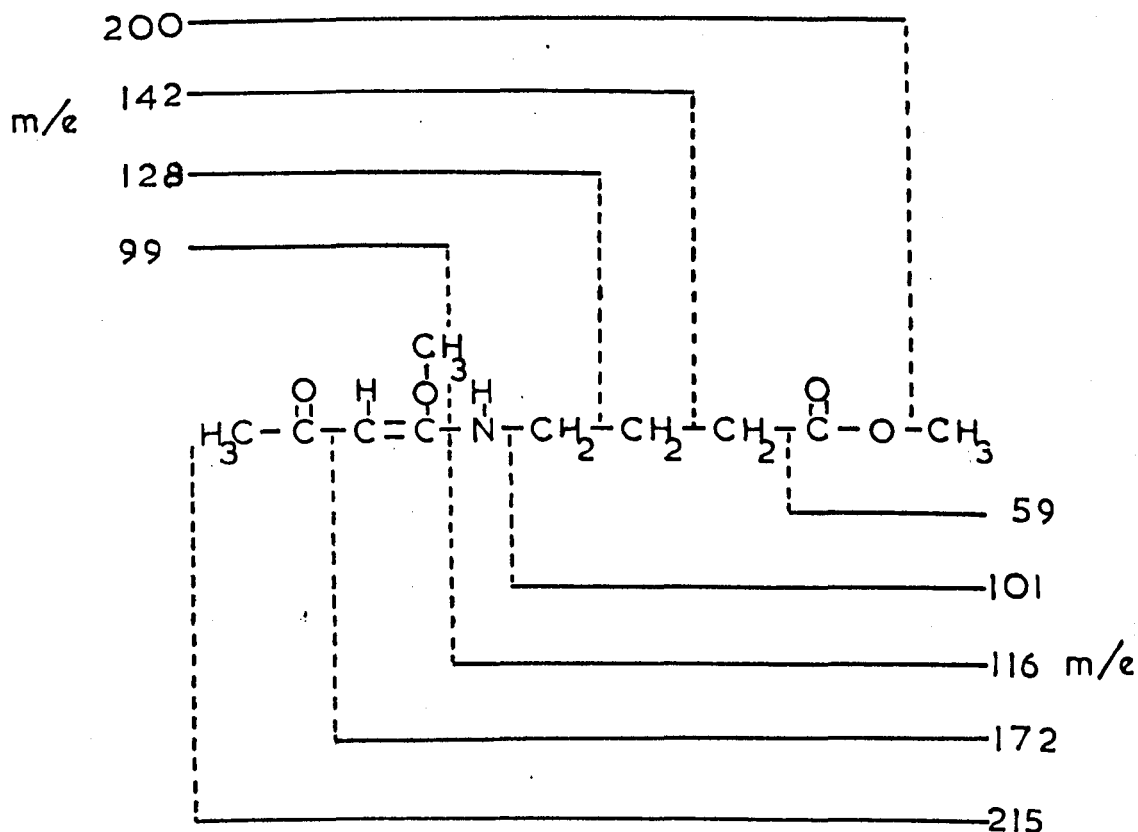
# Scheme 25





Mass Spectrum Of The  
Ketone (146).





The nuclear magnetic resonance spectrum (p.96) showed the three methyl groups as singlets at  $\delta$  2.02, 3.65 and 3.74 p.p.m. and the three methylene groups at  $\delta$  1.9, 2.3 and 3.3 p.p.m. The olefinic proton appeared as a sharp singlet at  $\delta$  4.72 p.p.m. and the amine proton as a broad exchangeable signal at  $\delta$  10.75 p.p.m.

To explain the products the nucleophile was considered to be methoxide ion which was generated from methanol by triethylamine. Sodium methoxide in methanol gave identical products. The reaction of the intermediate ketenimine (147) was thought to occur with the solvent methanol. An attempt was made to prove involvement of the solvent by treating the salt (94) with sodium methoxide in tert.-butanol.

N.m.r. Of The  
Ketone (146).

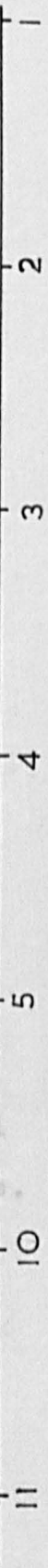
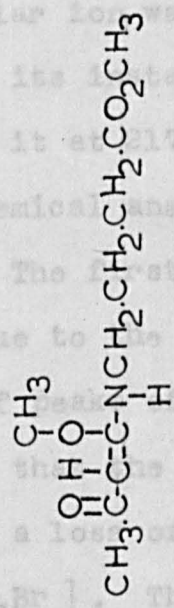
There was no ... and this was ascribed to the insolubility of the sodium methoxide in the butanol.

(1:1 3-(4-bromobutyl) isoxazole (146).

It was mentioned earlier (p. 85) that an initial band was eluted off the chromatography column after acetic anhydride treatment of salt (94); this was a very minor component isolated only in approximately 3% yield. The nuclear magnetic resonance spectrum (in CDCl<sub>3</sub>) had doublets at 8.72 and 8.52 p.p.m. due to the H4 and H5 of the isoxazole ring.

There was a four proton multiplet between 3.1-3.7 p.p.m. and a two proton multiplet between 2.1-2.5 p.p.m. The infrared spectrum had a strong carbonyl absorption at 1700 cm<sup>-1</sup> and an absorption due to the isoxazole ring at 1545 cm<sup>-1</sup>.

The molecular ion was not initially seen in the mass spectrum due to its instability but an appearance potential experiment gave it at 17 e/v with an M + 2 ion at 219 e/v. This and the chemical analysis gave the molecular formula as C<sub>7</sub>H<sub>9</sub>Br NO<sub>2</sub>. The first fragments seen in the mass spectrum were due to the cleavage at the carbonyl group giving a pair of fragments of equal intensity at 149 and 151 m/e showing that the fragments contained bromine. This represents a loss of the isoxazole ring to leave [C<sup>+</sup>CH<sub>2</sub>.CH<sub>2</sub>.CH<sub>2</sub>.Br]. The next fragments containing bromine appeared at 131, 133 m/e and are due to loss of



There was no apparent reaction and this was ascribed to the insolubility of the sodium methoxide in the butanol.

(iv) 3-(4-bromobutyryl) isoxazole (148).

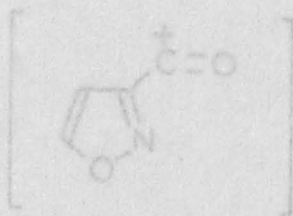
It was mentioned earlier (p.54) that an initial band was eluted off the chromatography column after the acetic anhydride treatment of salt (94); this was a very minor component isolated only in approximately 5% yield. The nuclear magnetic resonance spectrum (p.98) had doublets at  $\delta$  6.72 and 8.52 p.p.m. due to the H4. and H5. isoxazole ring protons which were coupled to each other ( $J = 2\text{Hz}$ ). There was a four proton multiplet between  $\delta$  3.1-3.7 p.p.m. and a two proton multiplet between  $\delta$  2.1-2.5 p.p.m. The infrared spectrum had a strong carbonyl absorption at  $1700\text{ cm}^{-1}$  and an absorption due to the isoxazole ring at  $1545\text{ cm}^{-1}$ .

The molecular ion was not initially seen in the mass spectrum due to its instability but an appearance potential experiment gave it at 217 m/e with an  $M + 2$  ion at 219 m/e. This and the chemical analysis gave the molecular formula as  $\text{C}_7\text{H}_8\text{Br NO}_2$ . The first fragments seen in the mass spectrum were due to the cleavage at the carbonyl group giving a pair of peaks of equal intensity at 149 and 151 m/e showing that the fragments contained bromine. This represents a loss of the isoxazole ring to leave  $[\text{O}^+\text{CCH}_2\text{.CH}_2\text{.CH}_2\text{.Br}]$ . The next fragments containing bromine appeared at 121, 123 m/e and are due to loss of

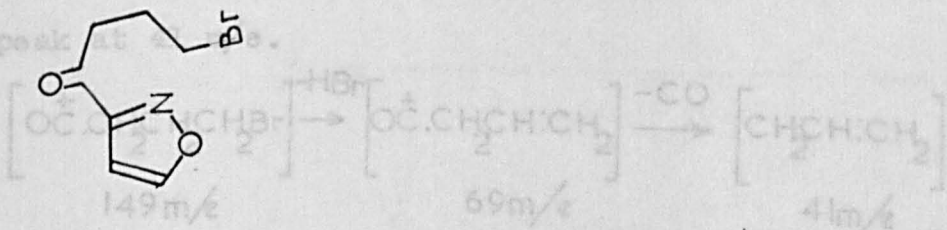
N.m.r. Spectrum Of

3-(4-bromobutyryl) Isoxazole (148).

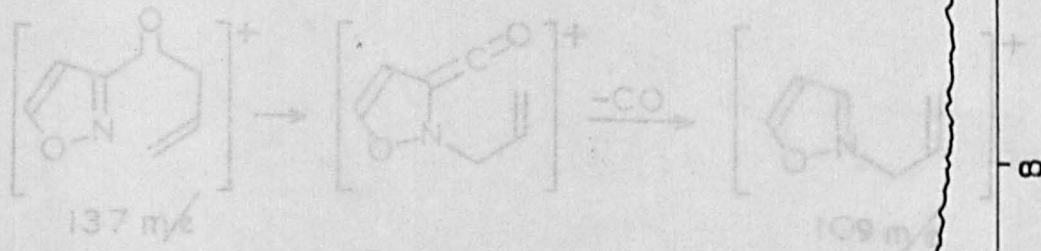
$[CH_2CH_2CH_2Br]$ . The molecular ion at 148 m/e was the only one which contained bromine since the isotope pattern was not seen anywhere else. The peaks at 137 and 138 m/e were due to the loss of hydrogen bromide and bromine atom respectively. The base peak at 96 m/e was due to the loss of the carbonyl group but with the loss of the side chain fragment to leave the very stable ion:



A large peak at 69 m/e may have arisen through the loss of hydrogen bromide from the fragment at 149 m/e which could in its turn lose carbon monoxide to give the other large peak at 41 m/e.



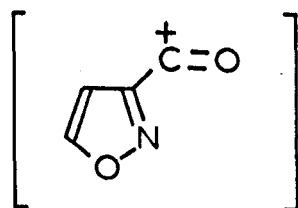
One of the remaining peaks to be assigned was the one at 109 m/e which may have arisen through a rearrangement of the fragment at 137 m/e as shown:



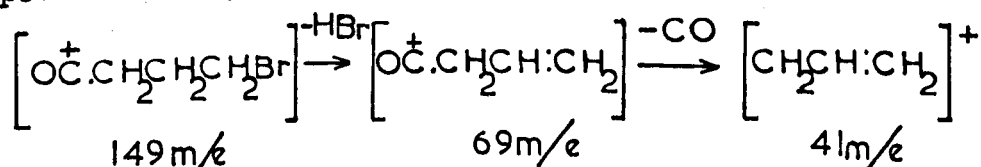
From this data the structure of the molecule was

carbon monoxide from the above to leave a fragment

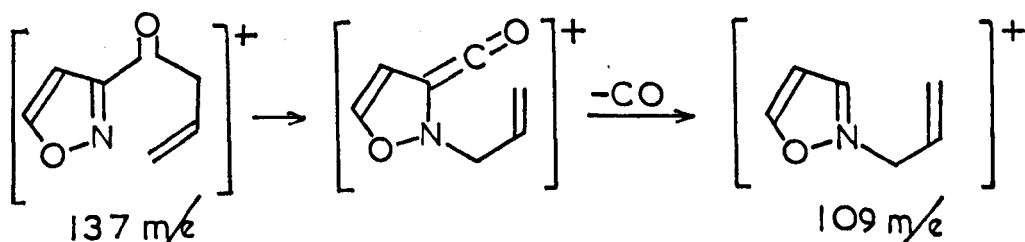
$[\dot{\text{C}}\text{H}_2.\text{CH}_2.\text{CH}_2.\text{Br}]^+$ . The molecular ion and these two fragments were the only ones which contained bromine since the isotope pattern was not seen anywhere else. The peaks at 137 and 138 m/e were due to the loss of hydrogen bromide and a bromine atom respectively from the molecular ion. The base peak at 96 m/e was due to cleavage at the carbonyl group but with the loss of the side chain fragment to leave the very stable ion:



A large peak at 69 m/e may have arisen through the loss of hydrogen bromide from the fragment at 149 m/e which could in its turn lose carbon monoxide to give the other large peak at 41 m/e.

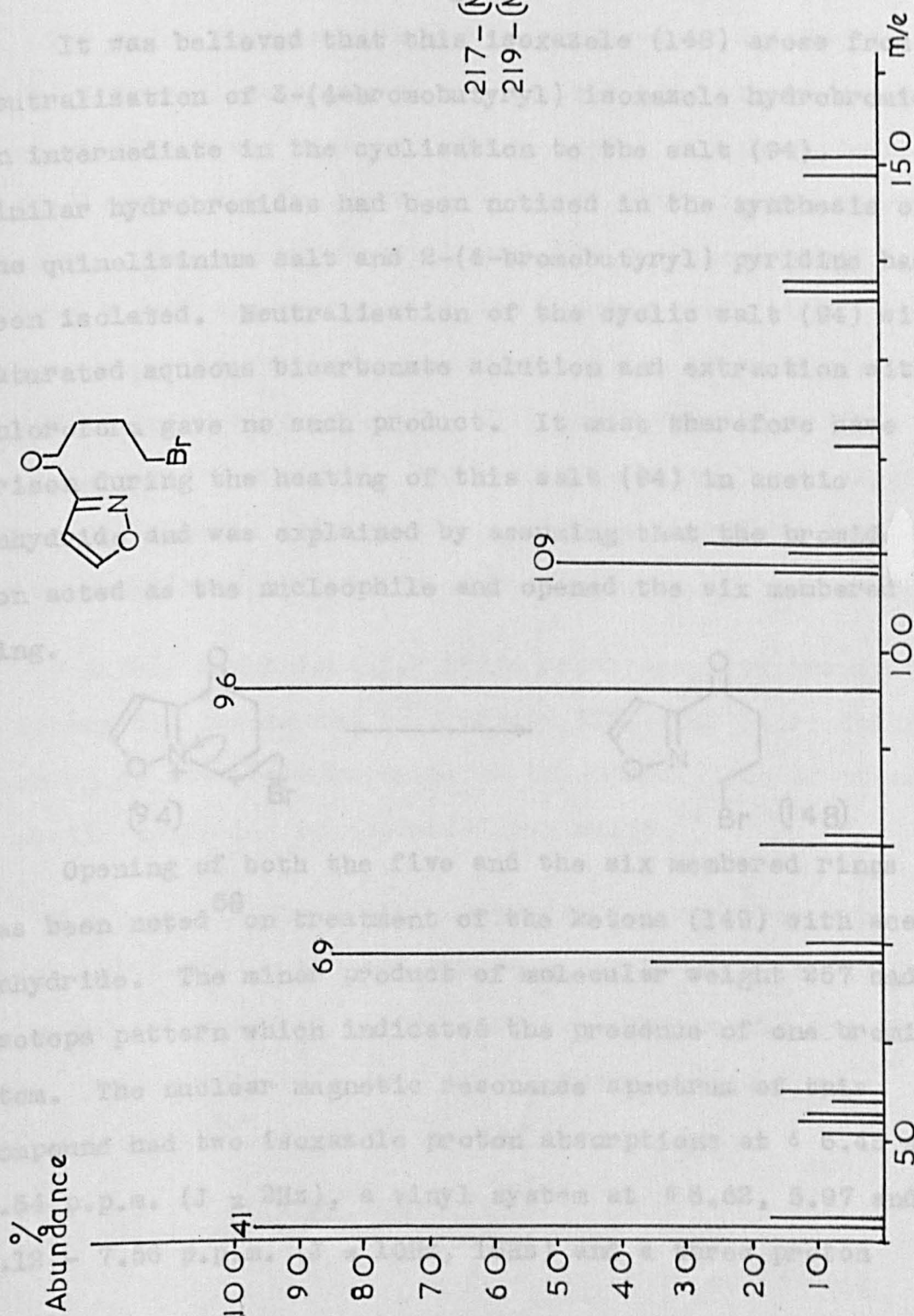


One of the remaining peaks to be assigned was the one at 109 m/e which may have arisen through a rearrangement of the fragment at 137 m/e as shown:

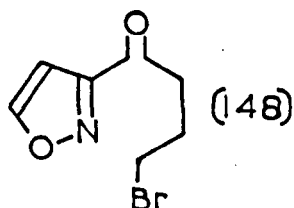


From this data the structure of the molecule was

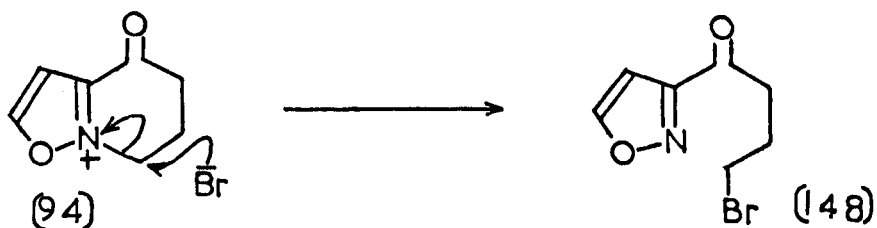


Mass Spectrum Of3-(4-bromobutyl) isoxazole (148).

assigned as 3-(4-bromobutyryl) isoxazole (148).



It was believed that this isoxazole (148) arose from neutralization of 3-(4-bromobutyryl) isoxazole hydrobromide, an intermediate in the cyclisation to the salt (94). Similar hydrobromides had been noticed in the synthesis of the quinolizinium salt and 2-(4-bromobutyryl) pyridine had been isolated. Neutralisation of the cyclic salt (94) with saturated aqueous bicarbonate solution and extraction with chloroform gave no such product. It must therefore have arisen during the heating of this salt (94) in acetic anhydride and was explained by assuming that the bromide ion acted as the nucleophile and opened the six membered ring.



Opening of both the five and the six membered rings has been noted<sup>58</sup> on treatment of the ketone (149) with acetic anhydride. The minor product of molecular weight 257 had an isotope pattern which indicated the presence of one bromine atom. The nuclear magnetic resonance spectrum of this compound had two isoxazole proton absorptions at  $\delta$  6.45 and 8.54 p.p.m. ( $J = 2\text{Hz}$ ), a vinyl system at  $\delta$  5.62, 5.97 and 7.12 - 7.56 p.p.m. ( $J = 10\text{Hz}, 16\text{Hz}$ ) and a three proton



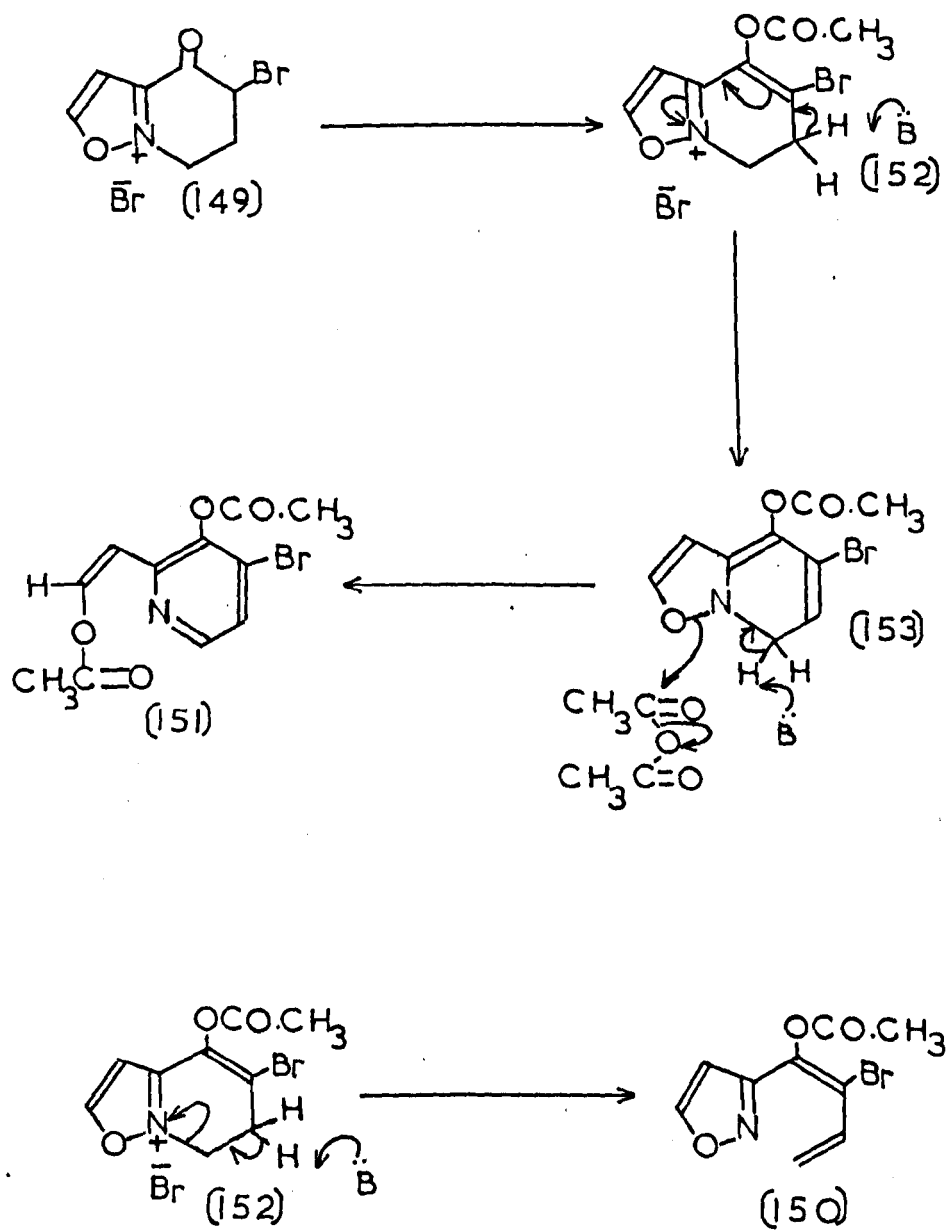
singlet. The infrared absorption at  $1770\text{ cm}^{-1}$  indicating an enolacetate carbonyl group and the nuclear magnetic resonance spectrum completed the evidence on which the structure of the isoxazole (150) was based.

The major product also had an enolacetate absorption in the infrared spectrum and the nuclear magnetic resonance spectrum showed the presence of two acetyl groups supported by the loss of two fragments of 42 mass units in the mass spectrum. The molecular weight was 299 and the isotope pattern showed the presence of one bromine atom. The nuclear magnetic resonance spectrum had two AB systems, one at  $\delta$  7.48 and 8.31 p.p.m. ( $J = 5\text{ Hz}$ ) which was due to the pyridine  $\alpha$  and  $\beta$  protons. The second AB system was associated with a cis-alkene; this spectral evidence therefore leads to the acetoxyvinylpyridine structure (151).

Possible mechanisms for these rearrangements are shown in scheme 21, the routes to products (150) and (151) following those which have been reported as the normal mode of attack by acetic anhydride on oxopyridinium salts.<sup>61</sup>

The normal route of the aromatisation reaction with acetic anhydride (p.53) via the enolacetate (152) to the uncharged intermediate (153) provides a way to the pyridine (151) by isoxazole ring opening. Hofmann elimination of the enolacetate (152) gave the isoxazole (150).

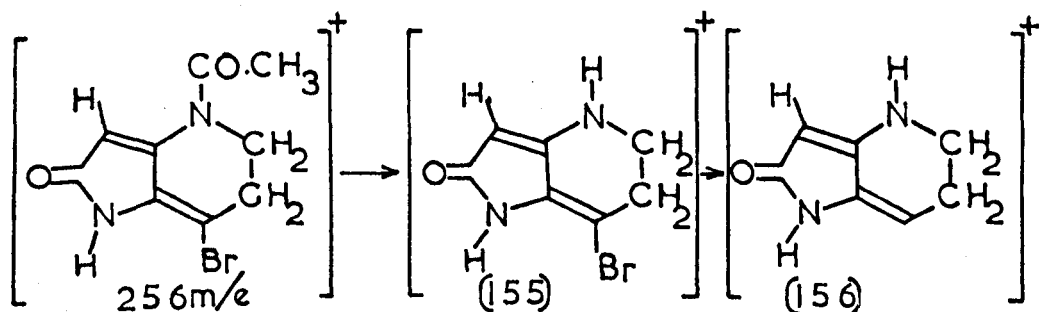
Scheme 21



(v) Pyrrolopyridones.

The oxime 4,5,6,7-tetrahydro-4-hydroximino isoxazolo [2,3-a] pyridinium bromide (154) was prepared by heating the salt (94) with hydroxylamine in ethanol. Percolation of a solution of the resultant product down an ion exchange column loaded with bromide ions ensured that all the anions were bromide. On treating the oxime (154) with boiling acetic anhydride it dissolved after a very short time. The reaction mixture was worked up as previously described for the rearrangement of salt (94).

The mass spectrum and chemical analysis of the major product gave the formula as  $C_9H_9BrN_2O_2$ . The first loss in the mass spectrum was ketene (42 mass units) which showed the presence of the acetyl group and giving ions (155) at 214 and 216 m/e. The only other ion (156) which appeared was the base peak at 135 m/e and resulted from the loss of a bromine atom from the ions at 214 and 216 m/e.



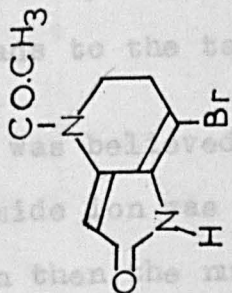
The nuclear magnetic resonance spectrum (p.105) showed a single proton as a broad exchangeable signal at  $\delta 8.52$  p.p.m. due to the amide hydrogen and the olefinic proton H3 as a singlet at  $\delta 6.0$  p.p.m. The methylene groups H5 and H6

N.m.r. Spectrum Of 4-Acetyl-7-bromo-

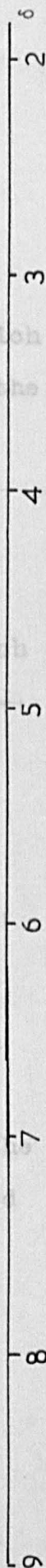
5,6-dihydro-4H-pyrrolo [3,2-b] pyrid-2-one (163).

2.31 p.p.m.

The favoured mechanism was the one postulating the ketene intermediate (p.107) although the one involving the isoxasoline could not be ruled out. The imino-amino tautomerism was thought to give the intermediate (157) which could undergo proton abstraction from position 2 to give the ketene intermediate (158). Nucleophilic attack by the nitrogen lone pair on the ketene group then gave the zwitterionic intermediate (159). Bond reorganisation and attack on acetic anhydride then gave the salt (160). The salt (160) could easily tautomerise to the salt (161) which lost water by a displacement with bromide. This displacement led to the tautomer (162) of the product (163).



It was believed that if the displacement of water by the bromide ion was the rate determining step of the reaction then the nucleophilicity of the anion may have a large effect on the yields. The chloride (164) and the iodide (165) were prepared by passing the salt (154) down the appropriate ion exchange columns. Acetic anhydride treatment of the chloride salt (164) gave approximately the same yield of rearrangement product (163) as that obtained from the bromide (154).

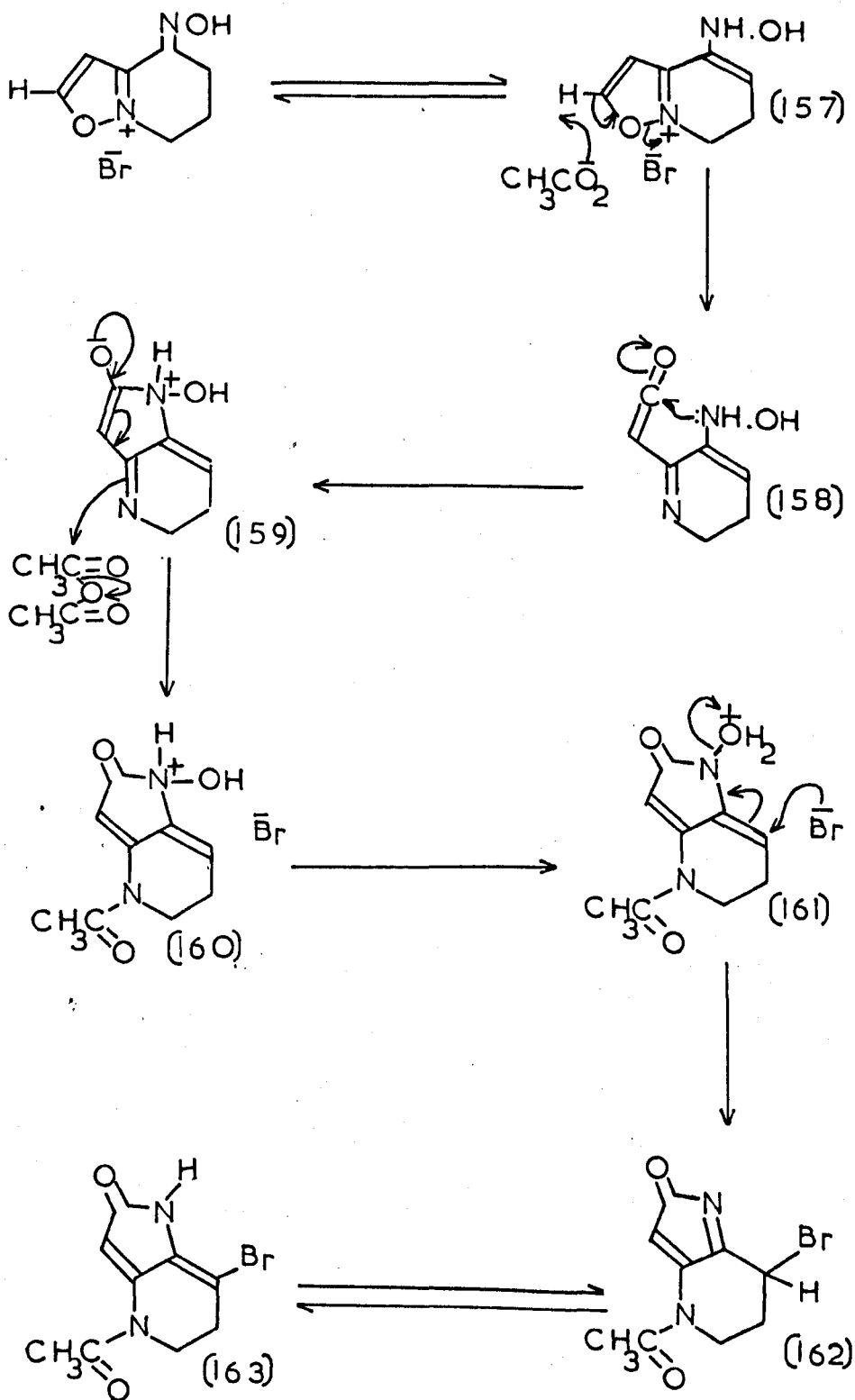


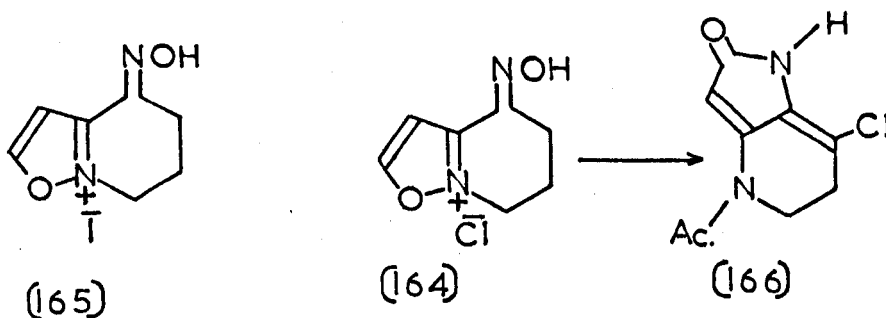
appeared as triplet absorptions at  $\delta$  3.98 and 2.82 p.p.m. and the three proton singlet of the methyl group at  $\delta$  2.31 p.p.m.

The favoured mechanism was the one postulating the ketene intermediate (p.107) although the one involving the isoxazoline could not be ruled out. The imino-amino tautomerism was thought to give the intermediate (157) which could undergo proton abstraction from position 2 to give the ketene intermediate (158). Nucleophilic attack by the nitrogen lone pair on the ketene group then gave the zwitterionic intermediate (159). Bond reorganisation and attack on acetic anhydride then gave the salt (160). The salt (160) could easily tautomerise to the salt (161) which lost water by a displacement with bromide. This displacement leads to the tautomer (162) of the product (163).

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Scheme 26



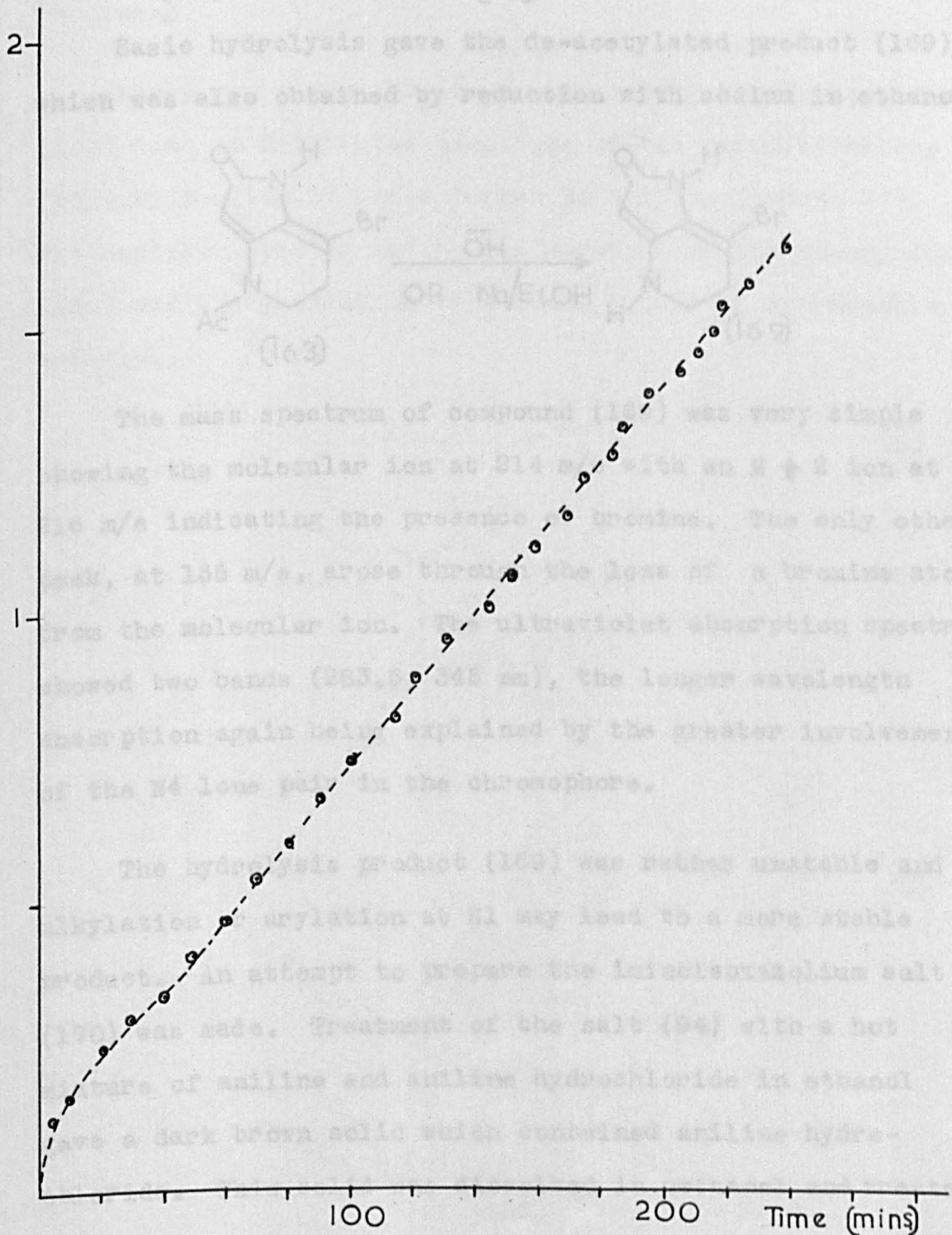


From treatment of the iodide (165) with acetic anhydride no product was isolated. Similar yields of products from the chloride (164) and the bromide (154) may indicate that the displacement was not rate determining. The sensitivity of salt (165) perhaps arose because of the reactivity of the product or because the iodide anion caused polymerisation of some reactive intermediate.

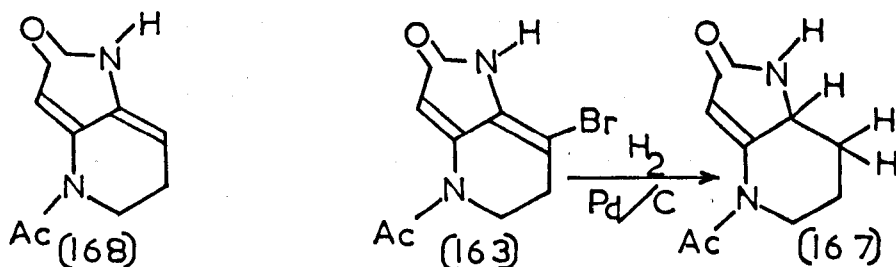
Reduction of the pyridone (163) using palladium on charcoal as the catalyst led to the uptake of two molar equivalents of hydrogen. Neutralisation and evaporation gave the dihydroderivative (167). It was hoped that the olefinic bond would reduce without reductive dehalogenation taking place so that dehydrohalogenation could be carried out to give the pyridone (168). The reduction was repeated and the uptake of hydrogen plotted against time (p.109) to see if it was a step-wise reduction. From the graph it could be seen that the hydrogen was taken up smoothly with no break at the one molar equivalent stage. An attempt to isolate a dihydroderivative containing a bromine atom was therefore abandoned.

Hydrogenation Of The  
Pyrrolopyridone (163).

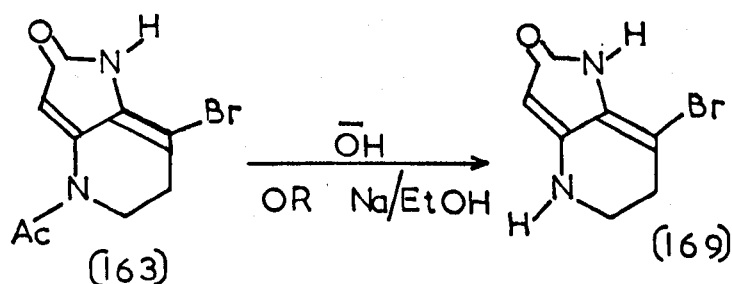
Mol./H<sub>2</sub>







Basic hydrolysis gave the de-acetylated product (169) which was also obtained by reduction with sodium in ethanol.

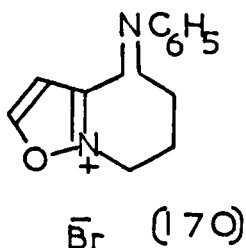


The mass spectrum of compound (169) was very simple showing the molecular ion at 214 m/e with an  $M + 2$  ion at 216 m/e indicating the presence of bromine. The only other peak, at 135 m/e, arose through the loss of a bromine atom from the molecular ion. The ultraviolet absorption spectrum showed two bands (283.5, 345 nm), the longer wavelength absorption again being explained by the greater involvement of the N4 lone pair in the chromophore.

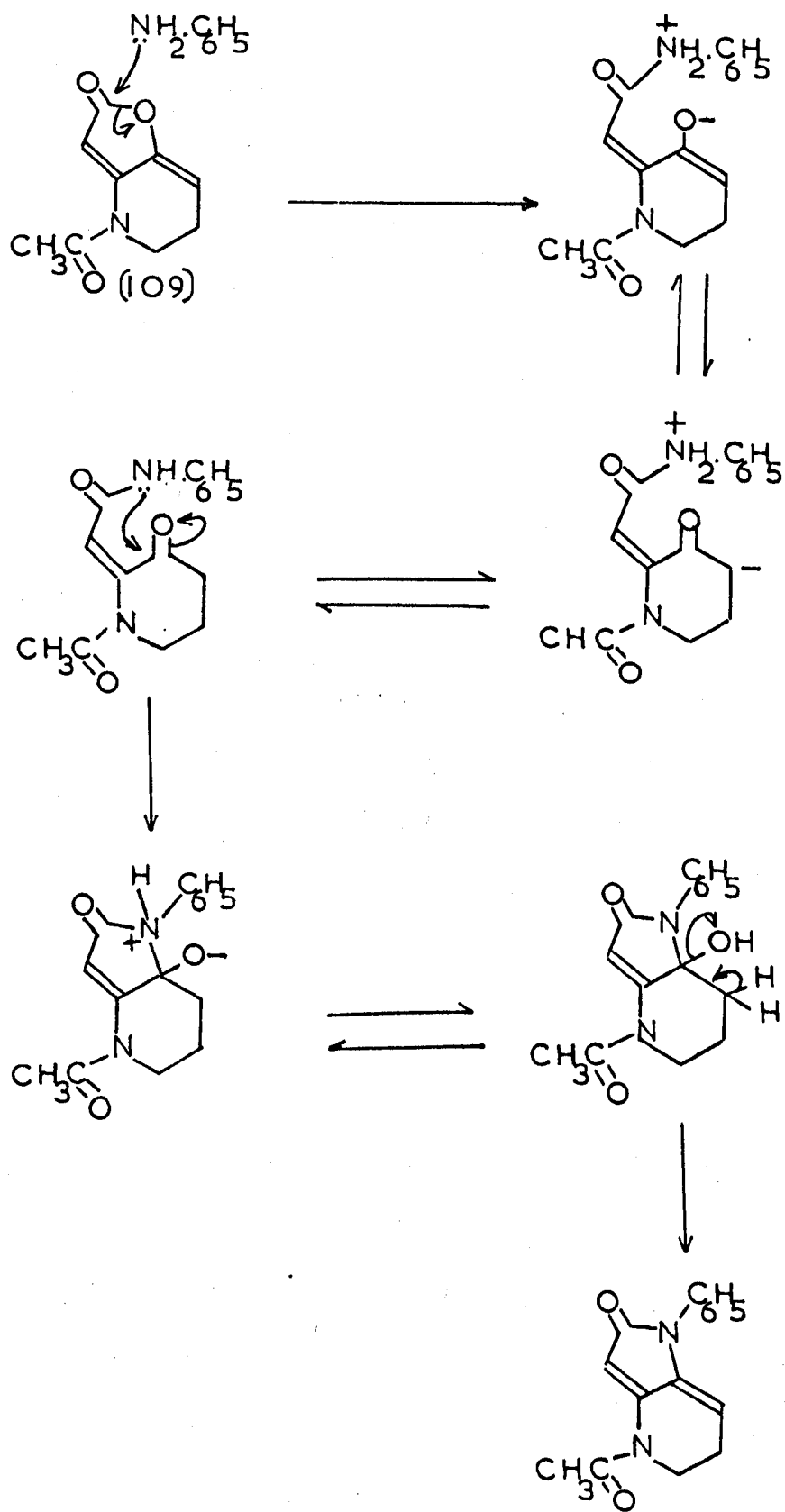
The hydrolysis product (169) was rather unstable and alkylation or arylation at N1 may lead to a more stable product. An attempt to prepare the iminoisoxazolium salt (170) was made. Treatment of the salt (94) with a hot mixture of aniline and aniline hydrochloride in ethanol gave a dark brown solid which contained aniline hydrochloride. This solid was dissolved in methanol and treated

with a weakly basic ion exchange resin in an attempt to liberate the aniline from its salt. After filtering off the resin, passage down an ion exchange column loaded with bromide ions and evaporation only starting material was recovered.

There was a possibility of converting the furopyridone (109) into an N-arylated homologue of the pyrrolopyridone (163) by heating it under reflux in aniline (scheme 27). The reaction however led to the recovery of the furopyridone (109) and the production of a small amount of intractable material.



Scheme 27



Experimental.

Preliminary Notes.

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

Infrared absorption spectra were measured on a Perkin Elmer 257 spectrophotometer and the  $\nu_{\max}$  values are quoted.

Electron absorption spectra were recorded on a Unicam SP 800 instrument. The  $\lambda_{\max}$  values are quoted with the extinction coefficient expressed as  $\log_{10} \epsilon$  in brackets.

Nuclear magnetic resonance (N. M. R.) spectra, unless otherwise stated were recorded on a Perkin Elmer R10 60MHz. instrument and are quoted as 'delta' ( $\delta$ ) values in p.p.m. using a tetramethylsilane standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet and br = broadened.

Microanalyses were carried out on an F and M carbon/hydrogen/nitrogen analyser at the University of Keele.

Mass spectra were determined on a Hatachi-Perkin Elmer RMU-6 instrument and the exact mass determinations were performed on an A.E.I. MS 902 machine.

Column chromatography was carried out using deactivated Woelm alumina.

Thin layer chromatography was carried out on

7.5 x 2.5 cm microscope slides coated with Kieselgel PF<sub>254</sub> (Merck). The components were visualised under ultraviolet light or developed in iodine vapour.

Preparative layer chromatography was carried out on 40 x 20 cm glass plates coated with a 1.5 mm layer of Kieselgel PF<sub>254</sub>. The separate components, visualised as for thin layer chromatography, were isolated by scraping off the silica and extracted with hot methanol. The filtered methanol solution was evaporated to leave a residue which contained silica. The residue was then dissolved in chloroform, filtered and evaporated.

Photolytic work was performed under an atmosphere of nitrogen using a Hanovia Photochemical reactor mainly transmitting light of 254, 265, 297, 313 and 366 nm. wavelength.

### 3-Ethoxycarbonylisoxazole (96).

To a boiling, vigorously stirred, solution of vinyl acetate (43g) and triethylamine (6g) in ether (200c.c.) was added carbethoxychloraldoxime (7.5g) in ether (50 c.c.)(over a period of 1 hour.). There was an immediate precipitation of triethylamine hydrochloride. After the complete addition, heating was continued for another hour, water (80 c.c.) added and the layers separated. The ether layer was dried (magnesium sulphate), filtered and the solvent removed. The crude product obtained was heated (1h.) at approximately

180°C. After all the acetic acid had been distilled off the product was distilled at reduced pressure. This method improves the overall yield to 90% (6.7g) as compared to 75% by the method described by R.G. Micetich.<sup>47</sup>

4-Acetyl-5,6-dihydro-4H-furo [3,2-b] pyrid-2-one (109) and 3-(4-bromobutyryl) isoxazole (148).

Attempts to improve the yield of the rearrangement product (109) by treating separate samples of 4,5,6,7-tetrahydro-4-oxoisoxazolo [2,3-a] pyridinium bromide (94) (0.5g) with acetic acid (30 c.c.), acetic acid/ acetic anhydride (1 mole)(30 c.c.), and acetic acid/acetic anhydride (50/50) and heating the mixtures under reflux failed, only the salt (94) was recovered. The yield of compound (109) was increased to 65% by heating the salt (94)(5g) in acetic anhydride just to its boiling point, cooling and decanting the solution from the unreacted salt (94). This process was repeated until all the salt had reacted, and the acetic anhydride was then distilled off under reduced pressure. Absolute ethanol was added to the dark brown viscous oil produced and distillation under reduced pressure eliminated the last traces of acetic anhydride. The crude product was percolated down an alumina (IV)(120g) column using benzene as the eluent. The first band isolated (200 c.c. benzene) contained the minor product 3-(4-bromobutyryl) isoxazole (0.25g, 5%). The major product (109)(2.46g, 60%) was collected in the next 400 c.c. of benzene.

The 3-(4-bromobutryl) isoxazole (148) had:

I.R. (CHCl <sub>3</sub> )	1700, 1600 cm <sup>-1</sup>
U.V. (95% EtOH)	240 nm (3.17)
Found	C, 38.90; H, 4.11; N, 6.40%
C <sub>7</sub> H <sub>8</sub> Br NO <sub>2</sub> requires	C, 38.55; H, 3.70; N, 6.42%
N.M.R. (CCl <sub>4</sub> )	4.1 (2H,q); 3.1-3.7(4H,m); 6.72 (1H,dJ = 2Hz); 8.52(1H,dJ = 2Hz) p.p.m.
Mass Spectrum (m/e)	219(M+2), 217(M <sup>+</sup> ), 151, 149, 138, 137, 123, 121, 111, 109, 96, 69, 41.

Attempted dehydrogenation of the furopyridone (109).

The furopyridone (109)(0.2g) was heated under reflux overnight in xylene in the presence of 10% Pd/C catalyst. The starting material was recovered unchanged.

Heating the furopyridone (109)(0.2g) under reflux in xylene with dicyano-dichloro-benzoquinone overnight also failed to yield a dehydrogenated product.

The action of dienophiles on the furopyridone (109).

Heating samples of the furopyridone (0.2g) in dimethylacetylene dicarboxylate (0.5g), with styrene (0.3g) in benzene or with tetracyanoethylene (0.4g) in benzene under reflux overnight produced no adducts and the starting material was recovered in each case.

Ethyl 2-piperidylacetate.

Ethyl 2-pyridylacetate was prepared by the method

described in Organic Syntheses<sup>54</sup> and reduced in glacial acetic acid using Adams' catalyst. On distillation of the product under reduced pressure a white unidentified deliquescent solid was obtained.<sup>55</sup> Reduction using the same solvent and catalyst but under a pressure of 90 lb ins<sup>-2</sup> gave the same solid. The picrate derivative of this solid was prepared and recrystallised from ethanol until pure. The piperidylacetate was then regenerated by dissolving the picrate in benzene and shaking with ammonium hydroxide solution. The amine remained in the benzene layer and was redistilled (60% recovery from the picrate). The ethyl 2-piperidylacetate could be produced directly from the white deliquescent solid by dissolving it in chloroform and washing the solution with ammonium hydroxide solution. This gave an 80% recovery of the required product. Overall yield from ethyl 2-pyridylacetate 55%

b.p.

78-80°C/0.1 mm Hg

Preparation of the azetidinone (112).

To an ether (50 c.c.) solution of the Grignard reagent from methyl iodide (11.1g) was added ethyl 2-piperidylacetate (5g) in ether (50 c.c.) and the mixture boiled (0.5h). The ether was separated from a tan coloured oil by decantation. The crude product was then dissolved in chloroform and washed successively with dilute hydrochloric acid and saturated ammonium chloride solution. The product was finally distilled under reduced pressure (1.17g, 32% b.p. 55-56°C/0.1 mm



Lit<sup>63</sup> b.p. 65-70°C/0.5 mm).

An attempt to improve the yield by inverse addition of the Grignard reagent to the amine solution gave an increased yield of the crude tan coloured product but a decrease in yield of the pure azetidinone (112).

Action of 2,3-dichloro-5,6-dicyano-benzoquinone on the azetidinone (112).

Heating the azetidinone (0.5g) with the quinone (1.0g) under reflux in benzene (24h.), filtration and evaporation gave a crude product from which no pure product was isolated.

Action of N-bromosuccinimide on the azetidinone (112).

The azetidinone (1g) and N-bromosuccinimide (1.5g) were added to carbon tetrachloride (30 c.c.) and heated under reflux with concomitant irradiation (5 mins). The solid succinimide was filtered off and the solvent distilled. The residue was dissolved in chloroform and washed with water. Distillation of the dry chloroform layer gave a residue which on elution up preparative layer chromatography plates using chloroform/10% methanol showed the presence of many components none of which were isolated in sufficient quantity to characterise. The majority of the material remained at the origin.

Hydrogenation of the azetidinone (112).

The azetidinone (1g) was dissolved in ethanol (95%,

100 c.c.) platinum oxide (0.1g) added and the solution hydrogenated at atmospheric pressure and room temperature. The product was separated on preparative layer chromatography plates using a chloroform/10% methanol mixture. Only one component was isolated and this had identical physical properties with the starting material.

Hydrolysis of the furopyridone (109).

Hydrolysis of the furopyridone (109) as previously described by Phipps, Good and Jones<sup>58</sup> gave very variable yields on a larger scale. The best reproducible yield was obtained by dissolving the furopyridone (109)(1g) in absolute ethanol (20 c.c.) and adding dilute sodium hydroxide solution (approximately 0.5 c.c.) until the reaction had gone to completion (seen by thin layer chromatography and ultraviolet spectroscopy). The solution was then neutralised with concentrated hydrochloric acid and the whole solution passed down an alumina (IV, 20g) column. Distillation of the solvent at reduced pressure and at room temperature gave the hydrolysis product (118) in a 90% yield (recrystallised from benzene).

Action of lead tetraacetate on the furopyridone (118).

The hydrolysed furopyridone (118)(0.3g) was dissolved in benzene (20 c.c.) and lead tetraacetate (3g) added, the solution was then heated under reflux (24h). The residue produced after distilling off the benzene was dissolved in

chloroform and washed with a dilute alkali solution. The chloroform extract was passed down an alumina (IV, 20g) column and gave a complex mixture of products (0.1g).

The alkaline aqueous layer was neutralised with acetic acid and re-extracted with chloroform. This extract (0.02g) contained a large number of components none of which were isolated.

4-Acetyl-3,7,7a-tribromo-5,6,7,7a-tetrahydro-4H-furo[3,2-b]pyrid-2-one (120).

To a solution of the furopyridone (109)(0.5g) and pyridine (0.25g) in dry chloroform (25 c.c.) was added a solution of bromine (1g) in dry chloroform (10 c.c.) over  $\frac{1}{2}$  h.

When four fifths of the bromine solution had been added an orange precipitate was obtained which disappeared after allowing the solution to stand at room temperature (16h.). The solvent was evaporated off and the residue dissolved in the minimum of hot, absolute ethanol. A product separated on cooling which was recrystallised from carbon tetrachloride to give the tribromo compound (120) which had m.p. 132-133°C (0.22g, 20%).

Found	C, 25.9; H, 2.28; N, 3.40%
$C_9H_8Br_3NO_3$ requires	C, 25.86; H, 1.93; N, 3.35%
I.R. ( $CHCl_3$ )	1790, 1690, 1640 $cm^{-1}$
U.V. (95% EtOH)	295 m.m. (3.76)
N.M.R. ( $CDCl_3$ )	2.8-3.8 (3H,m); 2.2 (3H,s); 4.4-4.85 (1H,m); 4.95 (1H,t) p.p.m.
Mass Spectrum (m/e)	421 (M + 6); 419 (M + 4); 417 (M + 2); 415 ( $M^+$ ).

#### Hydrolysis of the tribromo derivative (120).

The tribromo derivative (120)(0.3g) was dissolved in ethanol (95%, 100 c.c.) and sodium hydroxide (2N, 1 c.c.) solution added slowly until the solution was alkaline. The solution turned red when alkaline and on neutralisation with dilute hydrochloric acid changed to a pale yellow colour. Evaporation to dryness and extraction with absolute ethanol gave a crude mixture from which no products were isolated. Preparative layer chromatography indicated a large number of components with most of the material remaining at the origin.

#### Bromination of the furopyridone (109) with N-bromosuccinimide.

The furopyridone (109)(0.2g) was dissolved in chloroform containing N-bromosuccinimide (0.25g) and the mixture heated with concomitant irradiation ( $\frac{1}{2}$ h.). The solution was then cooled, evaporated to dryness and the residue extracted with deuteriochloroform. Thin layer chromatography and the nuclear magnetic resonance spectrum showed a mixture. From preparative layer chromatography only one product was isolated

(0.02g) whose structure was shown by its nuclear magnetic resonance spectrum to be 4-acetyl-3-bromo-5,6-dihydro-4H-furo[3,2-b]pyrid-2-one (123). Attempts to repeat this experiment have so far failed.

Compound (123) had the following:

N.M.R. ( $\text{CDCl}_3$ )                      2.28(3H,s); 2.45 (2H,m); 3.96(2H,t);  
5.83(1H,t) p.p.m.

5,6,7,7a-Tetrahydro-4H-furo[3,2-b]pyrid-2-one (125).

The furopyridone (118)(0.2g) was dissolved in ethanol (95%, 100 c.c.) and hydrogenated using Pd/C (10%, 0.05g) catalyst until the uptake of hydrogen had ceased ( 1 molar equivalent ). The solution was filtered, evaporated to dryness and the resultant solid recrystallised from benzene m.p. 119-120°C (0.2g, 98.5%). The physical data was identical with that obtained for compound (125) which had been prepared by hydrolysis of the dihydrofuropyridone (124).<sup>58</sup>

The production of 2-piperidylacetic acid from the furopyridone (118).

The furopyridone (118)(0.5g) was dissolved in ethanol (95%, 100 c.c.) and hydrolysed with dilute sodium hydroxide solution (0.2 c.c., 2N). This alkaline solution was hydrogenated with  $\text{PtO}_2$  (0.1g) as catalyst, two molar equivalents of hydrogen being absorbed. The catalyst was filtered off, the solution was neutralised and the solvent distilled off under reduced pressure. The resultant acid (127)

recrystallised from ethanol/ethyl acetate had m.p.  $214^{\circ}\text{C}$  (d)  
(Lit<sup>64</sup> m.p.  $212^{\circ}\text{C}$ )

Ethyl 2-piperidylacetate was prepared by bubbling hydrogen chloride gas through an ethanolic solution of the acid (127)(0.5g). The ester was isolated by distilling off the solvent and subsequent distillation under reduced pressure bp.  $125^{\circ}\text{C}/20\text{ mm.Hg}$  (Lit<sup>55</sup> bp.  $105^{\circ}\text{C}/14\text{ mm Hg}$ )(0.55g, 77%)

The 2-piperidylacetic acid was finally characterised by mixed melting point of the ethylester picrate with an authentic sample prepared from ethyl 2-pyridylacetate.

### 3-Ethoxycarbonyl-5-methylisoxazole (132).

Isopropenyl acetate (340g), ether (500 c.c.) and triethylamine (35g) were heated under reflux whilst carbethoxy-chloraldoxime (50g) in ether (200 c.c.) was added. Heating was continued for a further 2h. after the addition of the oxime. Water (200 c.c.) was then added and the two layers separated. The ether layer was dried (magnesium sulphate), filtered and the solvent removed. The resultant oil was heated ( $180^{\circ}\text{C}$ , 2h.) and the acetic acid so produced discarded. The product was then distilled under vacuum bp.  $140^{\circ}\text{C}/15\text{mm Hg}$  (15.5g, 30%)(Lit<sup>65</sup> bp.  $105^{\circ}\text{C}/10\text{mm Hg}$ ).

IR (Liquid film)	$3140, 1735\text{ cm}^{-1}$
U.V. (95% EtOH)	$243.5\text{ nm. (3.43)}$
N.M.R. ( $\text{CDCl}_3$ )	$1.4(3\text{H}, \text{t}); 2.5(3\text{H}, \text{s}); 4.4(2\text{H}, \text{q});$ $6.4(1\text{H}, \text{s})\text{ p.p.m.}$
Mass Spectrum (m/e)	$155 (\text{M}^+)$

3-Amido-5-methylisoxazole.

The ester (132)(15.5g) was dissolved in a small volume of methanol (30 c.c.) and added slowly to an ammonia solution (s.g. 0.88, 200 c.c.) at 0°C. The reaction mixture was kept at 0°C for three days and the product filtered off. The solute was evaporated to dryness and the solid obtained added to that previously collected. The amide had m.p. 166°C (8.2g, 65%)(Water)(Lit<sup>66</sup> m.p. 164°C).

Found	C, 47.30; H, 4.99; N, 22.5%
Calculated for $C_5H_6N_2O_2$	C, 47.61; H, 4.80; N, 22.22%
IR (Mull)	3380, 3190, 1670 $cm^{-1}$
U.V. (95% EtOH)	219 n.m. (3.66)
N.M.R. (T.F.A.)	2.6(3H,s); 6.7(1H,s); 8(2H,br.s)p.p.m.
Mass Spectrum (m/e)	126 ( $M^+$ )

3-Cyano-5-methylisoxazole (133).

A mixture of 3-amido-5-methylisoxazole (7g) and phosphorus pentoxide (14g) was heated to 160°C, when the pressure was reduced the nitrile (133) distilled 87-88°C/25 mm Hg. (3.6g, 60%)(Lit<sup>66</sup> bp 182°C/760 mm Hg)

IR (Liquid film)	3140, 2250 $cm^{-1}$
U.V. (95% EtOH)	237 nm (3.56)
N.M.R. ( $CDCl_3$ )	2.6 (3H,s); 6.5 (1H,s) p.p.m.
Mass Spectrum (m/e)	108 ( $M^+$ )

3-(4-Ethoxybutyryl)-5-methylisoxazole (134).

The Grignard reagent from 3-ethoxypropyl bromide (12g)

and magnesium (1.88g) in dry ether (100 c.c.) was added to a stirred solution of the nitrile (133)(6.1g) in dry ether at  $-5^{\circ}\text{C}$ . The mixture was then stirred overnight at room temperature. Ice cold 12N hydrochloric acid was added slowly, and the ether layer was separated and extracted with a further quantity of acid. The combined acid extracts were diluted (to dissolve solids), the solution was stirred (2h.) and then neutralised at  $0^{\circ}\text{C}$  with ammonia (s.g. 0.88). The mixture was extracted with ether and the ether layer dried, filtered and evaporated. The ketone (134) was distilled; bp.  $81-84^{\circ}\text{C}/0.2\text{ mm Hg}$  (7g, 63%).

Found	C, 60.5; H, 7.65; N, 7.2%
$\text{C}_{10}\text{H}_{15}\text{NO}_3$ requires	C, 60.9; H, 7.65; N, 7.1%
IR (Liquid film)	3140, 1700 $\text{cm}^{-1}$
U.V. (95% EtOH)	247 nm. (3.27)
N.M.R. ( $\text{CDCl}_3$ )	1.1(3H,t); 2.0(2H,q); 2.5(3H,s); 2.9-3.7(6H,m); 6.35(1H,s) p.p.m.

4,5,6,7-Tetrahydro-2-methyl-4-oxoisoxazolo [2,3-a] pyridinium bromide (130).

A solution of the ketone (134)(4.2g) in 48% hydrobromic acid (100 c.c.) was boiled (1.5h.). Evaporation under reduced pressure gave a gum, solidifying when triturated with acetone. Recrystallised from ethanol/ethyl acetate, the isoxazolopyridinium bromide (130) hydrate had m.p.  $> 300^{\circ}\text{C}$  (4.6g, 93%)

Found	C, 38.6; H, 4.95; N, 5.6%
$\text{C}_8\text{H}_{10}\text{Br NO}_2 \cdot \text{H}_2\text{O}$ requires	C, 38.4; H, 4.85; N, 5.6%



IR (Mull)	3190 $\text{cm}^{-1}$ (No C=O absorption)
U.V. (95% EtOH)	233.5, 290 nm. (3.83, 3.30)
N.M.R. (T.F.A.)	2.6 - 3.2 (4H,m); 2.8(3H,s); 5.0(2H,t); 7.2(1H,s) p.p.m.

The action of acetic anhydride on the salt (130).

The salt (130)(1g) was heated under reflux in acetic anhydride (300 c.c.) for two minutes. The solution was then cooled and the solvent removed, absolute ethanol was added and this also distilled off. The resultant tar was passed up preparative layer chromatography plates but no product was isolated.

3-Ethoxycarbonyl-4-methylisoxazole.

Prepared as described for the ester (132), but from n-propenylacetate, in 45% yield. 3-Ethoxycarbonyl-4-methylisoxazole had m.p. 55-56°C, bp. 165°C/18 mm. Hg.

Found	C, 54.5; H, 5.85; N, 9.10%
$\text{C}_7\text{H}_9\text{NO}_3$ requires	C, 54.2; H, 5.85; N, 9.05%
IR. ( $\text{CHCl}_3$ )	1730 $\text{cm}^{-1}$
U.V. (95% EtOH)	248 nm. (3.40)
N.M.R. ( $\text{CCl}_4$ )	1.5(3H,t); 2.3(3H,s); 4.5(2H,q); 8.4(1H,s) p.p.m.
Mass Spectrum (m/e)	155 ( $\text{M}^+$ )

3-Amido-4-methylisoxazole.

Prepared from 3-ethoxycarbonyl-4-methylisoxazole as described for 3-amido-5-methylisoxazole in 30% yield. The

yield was improved to 50% by dissolving the ester in methanol and saturating this solution with ammonia gas. After three days at 0°C the solvent was evaporated and 3-amido-4-methylisoxazole recrystallised from water m.p. 103-103.5°C.

Found	C,47.5; H,4.5; N,21.8%
$C_5H_6N_2O_2$ requires	C,47.6; H,4.8; N,22.2%
IR. (CHCl <sub>3</sub> )	3510, 3400, 1695 cm <sup>-1</sup>
U.V. (95% EtOH)	220 nm. (3.56)
N.M.R. (T.F.A.)	2.4(3H,s); 7.6-8.4(2H,br.s); 8.5(1H,s) p.p.m.
Mass Spectrum (m/e)	126 (M <sup>+</sup> )

3-Cyano-4-methylisoxazole.

Prepared as described for the nitrile (133), from 3-amido-4-methylisoxazole in 84% yield. The 3-cyano-4-methylisoxazole had bp. 80-83°C/30 mm. Hg;

IR. (Liquid film)	3130, 2250 cm <sup>-1</sup>
U.V. (95% EtOH)	247 nm. (3.48)
N.M.R. (CDCl <sub>3</sub> )	2.8(3H,s); 8.43(1H,s) p.p.m.
Mass Spectrum (m/e)	108 (M <sup>+</sup> )

3-(4-Ethoxybutyryl)-4-methylisoxazole.

Prepared from 3-cyano-4-methylisoxazole by the method used to prepare compound (134). The 3-(4-ethoxybutyryl)-4-methylisoxazole was prepared in 38% yield and had bp. 78-80°C/0.1 mm. Hg.

Found	C,60.7; H,7.75; N,7.1%
C <sub>10</sub> H <sub>15</sub> NO <sub>3</sub> requires	C,60.9; H,7.65; N,7.1%
IR. (Liquid film)	3120, 1700 cm <sup>-1</sup>
U.V. (95% EtOH)	253 nm. (3.29)
N.M.R. (CCl <sub>4</sub> )	1.15 (3H,t); 2.0(2H,m); 2.25(3H,s); 2.9-3.6(6H,m); 8.2(1H,s) p.p.m.

4,5,6,7-Tetrahydro-3-methyl-4-oxoisoxazolo [2,3-a]  
pyridinium bromide (131).

Prepared from 3-(4-ethoxybutyryl)-4-methylisoxazole by the method described for compound (130), in 53% yield, the 3-methylisoxazolopyridinium bromide (131) hemihydrate had m.p. >300°C.

Found	C,39.4; H,5.0; N,6.1%
2C <sub>8</sub> H <sub>10</sub> Br NO <sub>2</sub> .H <sub>2</sub> O requires	C,39.85; H,4.60; N,5.8%
IR. (Mull)	1725 cm <sup>-1</sup>
U.V. (95% EtOH)	237, 301 nm. (3.69, 3.22)
N.M.R. (T.F.A.)	2.4-3.3(4H,m); 2.52(3H,s); 6.05(2H,t); 8.9(1H,s) p.p.m.

4-Acetyl-5,6-dihydro-3-methyl-4H-furo [3,2-b] pyrid-2-one(135).

Prepared from the salt (131) as described for compound (109), the N-acetyl-3-methylfuropyridone (135) (30%) had m.p. 102-104°C.

Found	C,62.00; H,6.00; N,7.30%
C <sub>10</sub> H <sub>11</sub> NO <sub>3</sub> requires	C,62.15; H,5.75; N,7.25%
IR. (CHCl <sub>3</sub> )	1765, 1675, 1640 cm <sup>-1</sup>

U.V. (95% EtOH)	276 nm. (4.21)
N.M.R. (CDCl <sub>3</sub> )	2.0(3H,s); 2.3(3H,s); 2.6(2H,m); 4.0(2H,t); 5.8(1H,t) p.p.m.
Mass Spectrum(m/e)	193 (M <sup>+</sup> )

The action of sodium borohydride on the isoxazolopyridinium bromide salt (94).

The salt (94)(1g) was dissolved in ethanol (95%, 25 c.c.) and an ethanolic solution of sodium borohydride (0.56g) was added slowly at room temperature. The alkaline (pH. 8-9) solution was cooled and neutralised with hydrobromic acid (approximately 3 c.c.). The residue remaining after distilling off the solvent was extracted with a small volume of ethanol (10 c.c.) and filtered. The product obtained from trituration of the residue after evaporation of the ethanol from the filtrate was not purified. This product was soluble in organic solvents but did not move from the origin of an alumina (IV) chromatography column .

The action of sodium borohydride on 3-(4-ethoxybutyryl) isoxazole (99).

The ketone (99)(2g) in ethanol (95%, 25 c.c.) was treated with sodium borohydride (0.42g) in ethanol (95%, 25 c.c.) at room temperature. After allowing the mixture to stand ( $\frac{1}{2}$ h.) the solvent was removed and the residue extracted with chloroform. The dried (Mg SO<sub>4</sub>) chloroform extract was evaporated and 3-(4-ethoxy-3-hydroxybutyl) isoxazole distilled bp. 122-126°C/3 mm Hg (1.95g, 97%)

Found	C, 58.5; H, 8.43; N, 7.6%
$C_9H_{15}NO_3$ requires	C, 58.35; H, 8.16; N, 7.56%
IR. (Liquid film)	3380, 1560 $cm^{-1}$
U.V. (95% EtOH)	212.5 nm. (3.53)
N.M.R. ( $CDCl_3$ )	1.2(3H,t); 1.85(4H,m); 3.45(4H,m); 4.42(1H,br,s); 4.9(1H,t); 6.43(1H,d J = 2Hz); 8.38(1H,d J = 2Hz) p.p.m.
Mass Spectrum (m/e)	185 ( $M^+$ )

Attempted cyclisation of 3-(4-ethoxy-3-hydroxybutyl)  
isoxazole.

The above alcohol (0.8g) was heated under reflux in hydrobromic acid (48%, 50 c.c.) for two hours. The hydrobromic acid was then removed under reduced pressure and the resultant tar triturated with dry acetone. A brown hygroscopic solid was produced which was not purified. The solid did not rearrange in acetic anhydride.

3-Propionylisoxazole (144).

A solution of 3-cyanoisoxazole (6.9g) in dry ether (100 c.c.) was treated with the Grignard reagent from ethyl iodide (12.5g) and magnesium (1.95g) and worked up as described for the ketone (99) to give the isoxazole (144) bp. 74-75°C/18 mm Hg (4.77g, 51.5%). Analysis carried out on the semicarbazone derivative because the ketone (144) was too volatile.

Found	C,46.0; H,5.10; N,30.5%
$C_7H_{10}N_4O_2$ requires	C,46.15; H,5.52; N,30.76%
IR. (Liquid film)	$1700\text{ cm}^{-1}$
U.V. (95% EtOH)	237.5 nm. (3.29)
N.M.R. ( $CDCl_3$ )	1.2(3H,t); 3.1(2H,q); 6.77(1H,d $J=2\text{Hz}$ ), 8.53(1H,d $J=2\text{Hz}$ ) p.p.m.
Mass Spectrum (m/e)	125 ( $M^+$ )

Attempted quaternisation of the ketone (144).

Heating the ketone (144) with methyl iodide in a sealed tube gave a carbonaceous mass from which no products were isolated.

Heating the ketone (144) with benzyl bromide in sulpholane to  $38^\circ\text{C}$  for two weeks, treating with dry ethyl acetate and distilling gave an almost quantitative recovery of the starting material.

Acetic anhydride treatment of the ketone (144).

The ketone (144)(0.2g) was dissolved in concentrated sulphuric acid (0.5 c.c.) and this acid solution heated under reflux in acetic anhydride (30 c.c.) for 2 mins. The acid solution was then reduced in volume (10 c.c.), neutralised with aqueous bicarbonate solution, extracted with chloroform, dried, filtered and evaporated under reduced pressure. The residue (0.04g) was dissolved in  $CDCl_3$  and a nuclear magnetic resonance spectrum obtained. This indicated a mixture of the ketone (144) and its enol

acetate.

N.M.R. ( $\text{CDCl}_3$ )      Ketone (144)    1.2(3H,t); 3.1(2H,q);  
6.75(1H,d J = 2Hz);  
8.5(1H,d J = 2Hz) p.p.m.

Enol acetate of ketone (144)    1.75(3H,d J=7Hz); 2.28(3H,s);  
6.14(1H,q J = 7Hz); 6.39(1H,d J=2Hz);  
8.32(1H,d J = 2Hz).p.p.m.

Attempted preparation of 3-(4-ethoxy-2-benzylbutyryl)  
isoxazole.

A solution of 3-(4-ethoxybutyryl) isoxazole (99)(4g) in dimethoxyethane was added to a suspension of sodium hydride (1.2g) in dimethoxyethane and heated under reflux (1h.) in an atmosphere of nitrogen. The solution was then cooled to 0°C and benzyl bromide added slowly. The solution was then stirred ( $\frac{1}{2}$ h.) at 0°C and boiled (24h.). Distillation of the solvent and column chromatography (Alumina IV, 20g,  $\text{C}_6\text{H}_6$ ) gave a crude product (0.52g) which the mass spectrum indicated was almost entirely benzyl bromide. Elution of the column with ethanol produced no further products.

3-(5-Ethoxyvaleryl) isoxazole.

A solution of 3-cyanoisoxazole (6.9g) was treated with the Grignard reagent from ethoxybutyl bromide (14.7g) and magnesium (2.13g) and worked up as described for the isoxazole (99) giving 3-(5-ethoxyvaleryl) isoxazole bp. 85°C/0.2 mm. Hg. (4.05g, 27%)

Found	C, 60.50; H, 7.54; N, 7.00%
$C_{10}H_{15}NO_3$ requires	C, 60.89; H, 7.67; N, 7.10%
IR. (Liquid film)	$1700\text{ cm}^{-1}$
U.V. (95% EtOH)	239 nm. (3.22)
N.M.R. ( $CCl_4$ )	1.13(3H,t); 1.5-2.0(4H,m); 2.9-3.7(6H,m); 6.7(1H,d $J=2\text{Hz}$ ); 8.53(1H,d $J=2\text{Hz}$ ).p.p.m.

Attempted cyclisation of 3-(5-ethoxyvaleryl) isoxazole.

The 3-(5-ethoxyvaleryl) isoxazole (2g) was heated under reflux in hydrobromic acid (100 c.c., 40%, 1h.). The work up as described for the salt (94) gave an oil, insoluble in organic solvents which could not be purified and which did not give an isolated rearrangement product after heating with acetic anhydride.

The action of nucleophiles on salt (94).

The salt (94)(1g) was treated with aqueous sodium bicarbonate (0.8g in 10 c.c.  $H_2O$ ) and the solution kept at room temperature (48h.). No non-ionic material was isolated on extraction with chloroform.

Similarly the salt (94)(1g) suspended in acetonitrile and treated with a mixture of glacial acetic acid (0.28g) and triethylamine (0.47g) at room temperature gave no products which moved on thin layer chromatograms on elution with methanol.



The salt (94)(1g) was dissolved in methanol (30 c.c.) and triethylamine (1.5 c.c.) added whilst the solution was heated under reflux. A thin layer chromatogram was run immediately after the addition of the triethylamine which indicated that a reaction had occurred almost instantaneously. The solvent was removed under vacuum and the residue triturated with dry acetone. The triethylamine hydrobromide was filtered off and the acetone evaporated. The resultant tar was passed down an alumina (IV, 40g) column with chloroform and the product isolated from the first 150 c.c. of eluent.

An identical product was obtained using sodium methoxide in methanol instead of the triethylamine.

<u>Vinylogous amide</u> (145)	0.52g (56%)
IR. (Liquid film)	1730, 1625, 1575 $\text{cm}^{-1}$
U.V. (95% EtOH)	292 nm. (4.31)
N.M.R. ( $\text{CCl}_4$ )	1.9(2H,q); 2.28(2H,m); 3.30(2H,q); 3.60(3H,s); 3.75(3H,s); 4.55(1H,d $J=4\text{Hz}$ ); 8.85(1H,d $J=4\text{Hz}$ ); 10.5(1H,br.s)p.p.m.
Mass Spectrum (m/e)	201( $\text{M}^+$ ); 184, 170, 142, 128, 116, 114, 101, 100, 84, 82, 69, 59.

Treatment of salt (130) with triethylamine in methanol.

The salt (130)(1g) was dissolved in methanol (30 c.c.) and whilst the solution was heated under reflux triethylamine (1.5 c.c.) was added. The ketone (146) was isolated as described above bp.  $110^\circ\text{C}$  0.1 mm Hg (0.61g, 67%)

Found	C,55.4; H,7.68; N,6.4%
$C_{10}H_{17}NO_4$ requires	C,55.80; H,7.96; N,6.51%
IR. (Liquid film)	1735, 1625 $cm^{-1}$
U.V. (95% EtOH)	289.5 nm. (5.30)
N.M.R. ( $CDCl_3$ )	1.9(2H,m); 2.02(3H,s); 2.3(2H,m); 3.3(2H,q); 3.65(3H,s); 3.75(3H,s); 4.72(1H,s); 10.75(1H,br.s) p.p.m.
Mass Spectrum (m/e)	215( $M^+$ ); 200, 172, 149, 142, 128, 124, 116, 101, 99, 86, 69, 59.

4-Hydroximino-4,5,6,7-tetrahydroisoxazolo[2,3-a]pyridinium salts (154, 164, 165).

A solution of sodium acetate (3g) and hydroxylamine hydrochloride (3g) in absolute ethanol were mixed together and the precipitated sodium chloride filtered off. The salt (94)(3g) was added and the solution boiled ( $\frac{1}{2}$ h.). Evaporation to a small volume followed by cooling gave a precipitate which was filtered off. An ethanolic solution of this precipitate was passed through a column of Amberlite IRA 400 (Br) resin and the eluted salt obtained by evaporation of the ethanol recrystallised from ethanol to give the oxime bromide (154) mp. > 300°C (2.2g, 69%)

Found	C,36.20; H,4.30; N,12.0%
$C_7H_9BrN_2O_2$ requires	C,36.10; H,3.90; N,12.0%
IR. (Mull)	1620, 1580 $cm^{-1}$
U.V. (95% EtOH)	266.5, 237.5 nm (4.03, 3.88)
N.M.R. ( $D_2O$ )	2.3(2H,m); 2.85(2H,m); 4.65(2H,t under HDO); 7.35(1H,d $J=2Hz$ ); 9.0(1H,d $J=2Hz$ ) p.p.m.

By substituting an Amberlite IRA 400 (Cl) column in the work up the oxime chloride (164) was obtained m.p. > 300°C (0.96g, 60%).

Found	C, 43.50; H, 4.87; N, 14.30%
$3C_7H_9Cl \cdot N_2O_2 \cdot H_2O$ requires	C, 43.20; H, 5.00; N, 14.40%
IR. (Mull)	1620, 1580 $cm^{-1}$
U.V. (95% EtOH)	266, 237 nm. (4.02, 3.90)
N.M.R. ( $D_2O$ )	2.3 (2H, m); 2.85 (2H, m); 4.65 (2H, t under HDO); 7.35 (1H, d J = 2Hz); 9.0 (2H, d J = 2Hz) p.p.m.

By substituting an Amberlite IRA 400 (I) column in the work up the oxime iodide (165) was obtained m.p. 199-200°C (1.44g, 60%).

Found	C, 30.6; H, 3.3; N, 9.5%
$C_7H_9I \cdot N_2O_2$ requires	C, 30.0; H, 3.2; N, 10.0%
IR. (Mull)	1620, 1580 $cm^{-1}$
U.V. (95% EtOH)	266.5, 222 n.m. (4.04, 4.20)
N.M.R. ( $D_2O$ )	2.3 (2H, m); 2.85 (2H, m); 4.65 (2H, t under HDO); 7.35 (2H, d J = 2Hz); 9.0 (2H, d J = 2Hz) p.p.m.

4-Acetyl-7-bromo-5,6-dihydropyrrolo [3,2-b] pyrid-2-one (163).

The oxime bromide (154) (5.4g) was heated in acetic anhydride to the boiling point of the solvent, then cooled and the solvent evaporated. The dark brown viscous oil obtained was dissolved in absolute ethanol and this was again evaporated. The residue was chromatographed on alumina

(IV, 120g) in benzene, evaporation of the solvent gave the N-acetyl pyrrolopyridone (163) m.p. 188-193°C (d) (from benzene)(2g, 33.6%).

Found	C,42.2; H,3.5; N,10.7%
$C_9H_9Br N_2O_2$ requires	C,42.0; H,3.5; N,10.9%
IR. ( $CHCl_3$ )	3430, 1690, 1590 $cm^{-1}$
U.V. (95% EtOH)	291.5 nm. (4.28)
N.M.R. ( $CDCl_3$ )	2.31(3H,s); 2.82(2H,t); 3.98(2H,t); 6.0(1H,br.s); 8.61(1H,br.s) p.p.m.
Mass Spectrum (m/e)	258(M+2), 256(M <sup>+</sup> ).

4-Acetyl-7-chloro-5,6-dihydropyrrolo [3,2-b] pyrid-2-one(166).

Prepared in a similar manner to the pyridone (163) from the oxime chloride (164), the pyrrolopyridone (166) had mp. 215-217°C (d) (from benzene)(30%).

Found	C,50.8; H,4.4; N,13.0%
$C_9H_9Cl N_2O_2$ requires	C,50.83; H,4.27; N,13.18%
IR. (Mull)	3190, 1670, 1575 $cm^{-1}$
U.V. (95% EtOH)	290 nm. (4.10)
N.M.R. ( $CDCl_3$ )	2.35(3H,s); 2.75(2H,t); 4.0(2H,t); 6.0(1H,br.s); 8.4(1H,br.s) p.p.m.
Mass Spectrum (m/e)	214(M+2), 212(M <sup>+</sup> ).

Attempted rearrangement of the iodide (165) in acetic anhydride.

Treating the salt (165) in the same way as the bromide (154) gave only an intractable tar from which no products were isolated.

4-Acetyl-5,6,7,7a-tetrahydro-4H-pyrrolo [3,2-b] pyrid-2-one (167).

A solution of the pyrrolopyridone (163)(1g) in ethanol (95%, 100 c.c.) was hydrogenated using Pd/C(0.1g) as catalyst until no more hydrogen was absorbed (2 molar equivalents). The solution was neutralised with sodium bicarbonate, filtered and the solvent evaporated under reduced pressure. The hydrogenated product (167) had mp. 182-184°C (0.65g, 93%) (from benzene).

Found	C,59.7; H,6.8; N,15.4%
C <sub>9</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> requires	C,60.0; H,6.7; N,15.6%
IR. (Mull)	3200, 1680, 1625 cm <sup>-1</sup>
U.V. (95% EtOH)	266, 234 nm. (3.94, 3.87)
N.M.R. (T.F.A.)	1.5-3.0(4H,m); 2.5(3H,s); 4.0(2H,t); 4.5-4.9(1H,m); 6.7(1H,s) p.p.m.
Mass Spectrum (m/e)	180(M <sup>+</sup> ).

5,6-Dihydro-4H-pyrrolo [3,2-b] pyrid-2-one (169).

To the pyrrolopyridone (163)(0.5g) in ethanol (95%, 100 c.c.) was added dilute caustic soda solution. When the hydrolysis was complete (shown by thin layer chromatography) the solution was neutralised with hydrochloric acid and then evaporated to dryness. The resultant solid was extracted with chloroform, filtered and evaporated to dryness to give the hydrolysis product (169), mp. >300°C (0.17g, 40%).

Precise Mass Measurement	213.9744
C <sub>7</sub> H <sub>7</sub> <sup>79</sup> Br N <sub>2</sub> O requires	213.9742

IR. (Mull)	3170, 1660, 1610 $\text{cm}^{-1}$
U.V. (95% EtOH)	283.5, 345 nm. (4.33, 3.54)
N.M.R. (T.F.A.)	3.3(2H,m); 4.17(3H,m); 9.6(1H,br.s) p.p.m.
Mass Spectrum (m/e)	216(M+2), 214(M <sup>+</sup> )

An identical product was obtained when the pyrrolo-pyridone was treated with sodium in dry ethanol (38%).

Treatment of the salt (94) with aniline/aniline hydrochloride.

The salt (94)(2g) was dissolved in absolute ethanol (100 c.c.), aniline (0.85g) and aniline hydrochloride (0.5g) added. The solution was heated under reflux (4h.), allowed to stand overnight and then the solvent evaporated. The solid obtained was dissolved in methylated spirits and shaken with a weakly basic ion exchange resin IR 4B (OH) . The solvent was removed after filtration and the solid obtained redissolved and passed down an IRA 400 (Br) column. The starting material (94) was recovered unchanged.

The action of aniline on 4-acetyl-5,6-dihydro-4H-furo[3,2-b]pyrid-2-one (109).

The pyridone (109)(0.5g) was dissolved in aniline (5 c.c.) and the solution heated under reflux. The reaction was followed by thin layer chromatography i.e. a few drops of the aniline solution were added to an excess of hydrochloric acid (2N) and the products extracted with chloroform. After heating under reflux (4h.), distilling off the aniline and

washing a solution of the residue in chloroform with hydrochloric acid (2N) only starting material (109) was recovered.

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## PART II

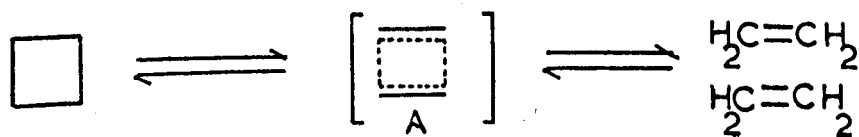
# Introduction.

During the attempts to establish the structure of the furopyridone (109) the rearrangement products were photolysed. They underwent [2+2] cycloadditions to give dimers and what appeared to be electrocyclic ring opening reactions.

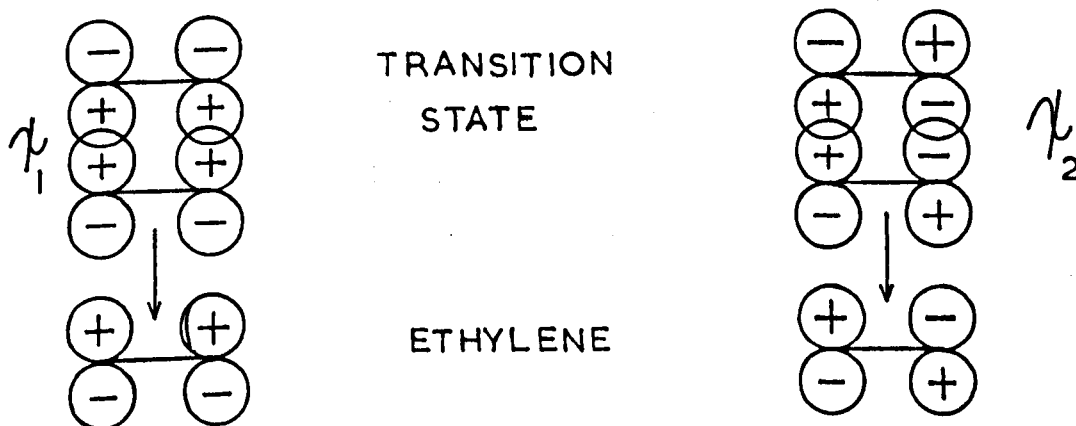
A cycloaddition reaction is a concerted, usually intermolecular process which involves the conversion of two  $\pi$  bonds into two  $\sigma$  bonds or the reverse process. For cycloaddition reactions the Woodward-Hofmann rules stipulate that the process is thermally forbidden and photochemically allowed when  $K = 4n$  (where  $K$  is the number of  $\pi$  electrons involved and  $n$  is an integer). The reverse is true when  $K = 4n+2$ .

In thermal cycloaddition reactions ( $n\sigma \rightarrow n\pi$ ) the transformation is allowed when the  $\sigma$  bonds being broken do so in such a way that the resultant p orbitals have the symmetry of the highest occupied molecular orbital of the ground state of the products.

Consider cyclobutane opening to give two ethylene molecules and that the transition state 'A' is weighted towards cyclobutane. That is, that the  $\pi$  bonds are almost



lost and that there is almost complete  $\sigma$  bond formation. There must be two molecular orbitals since four  $\pi$  electrons are involved. The two generalised molecular orbitals for the transition state are shown, they do not represent  $Sp^3$  or p orbitals but some stage between the two.



For the process to be thermally allowed the transition state must be bonding with respect to the fragments that it produces. It can be seen that if the symmetry is to be maintained an excited state ethylene would be obtained which is thermally not allowed but may be produced photochemically.

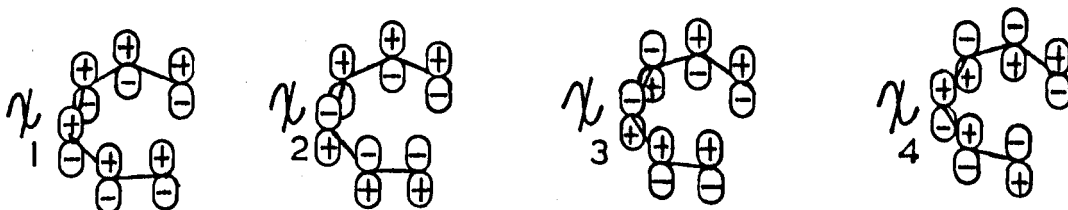
From the above it would be expected that isolated double bonds would only dimerise to cyclobutane photochemically and that if a cyclobutane ring is produced it would not open thermally.

An electrocyclic transformation is one in which a molecule with a system of  $n\pi$  electrons is converted into a ring system with  $(n-2)\pi$  electrons and a  $\sigma$  bond in a

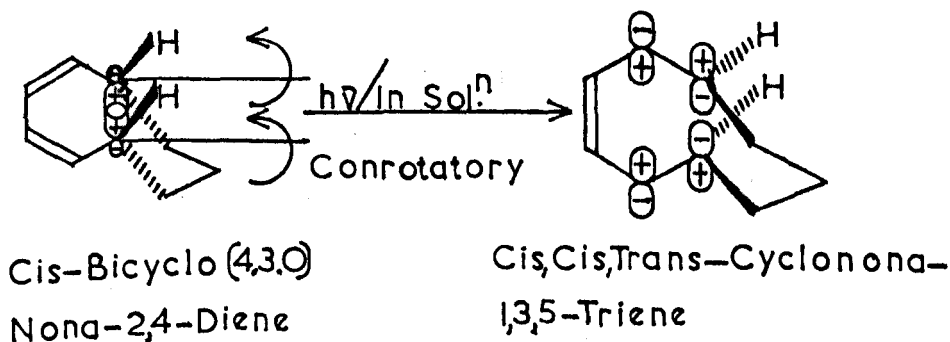
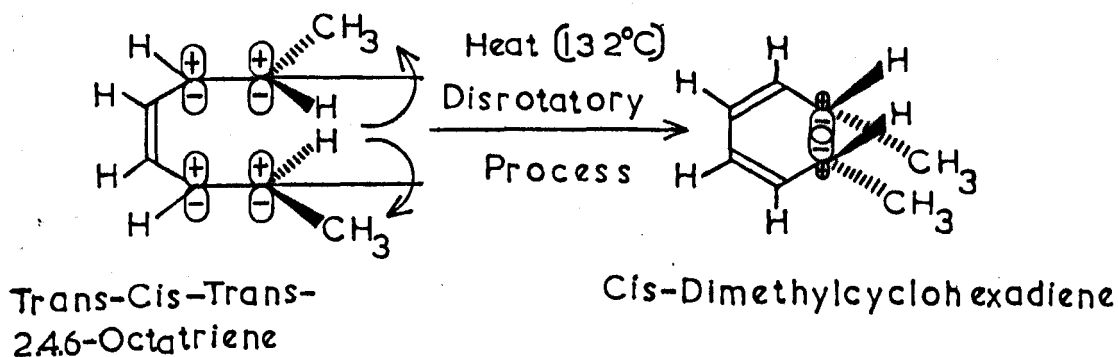


concerted manner or the reverse process.

The hexatriene system<sup>67,68,69</sup> has six  $\pi$  electrons which can be accommodated in the three molecular orbitals  $\psi_1$ ,  $\psi_2$  and  $\psi_3$ . The level which would be occupied on photochemical excitation  $\psi_4$  is the first antibonding state.



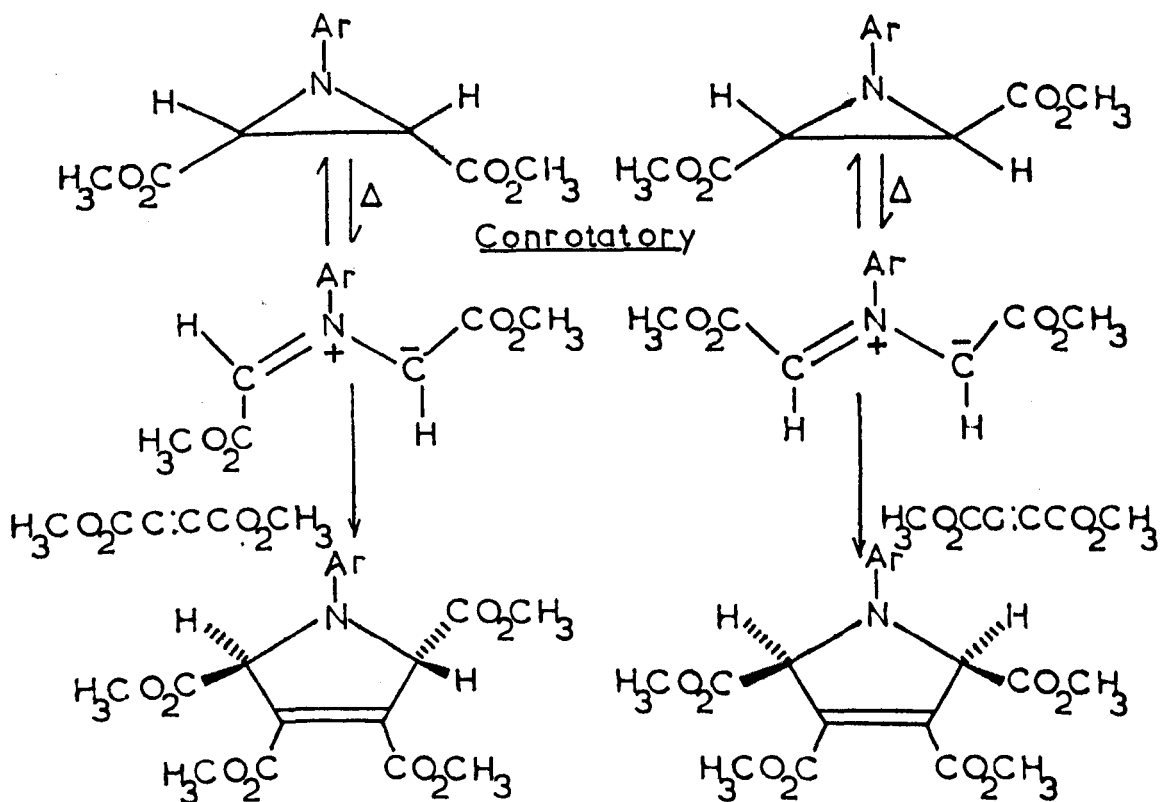
From the highest filled ground state molecular orbital ( $\psi_3$ ) it can be seen that ring closure (by a thermal process) would occur in a disrotatory manner. The photochemical reaction, where the first antibonding orbital ( $\psi_4$ ) is important would occur by a conrotatory process. These statements are supported by the examples<sup>70</sup> shown below:-



Electrocyclic transformations are thermally, symmetry allowed when the  $\sigma$  bond can be broken in such a way that the resultant p orbitals will have the symmetry of the highest occupied molecular orbital of the product, in this case  $\psi_3$ . For photochemical processes the  $\sigma$  bond must be broken so that the resultant p orbitals have the symmetry of the first excited state.

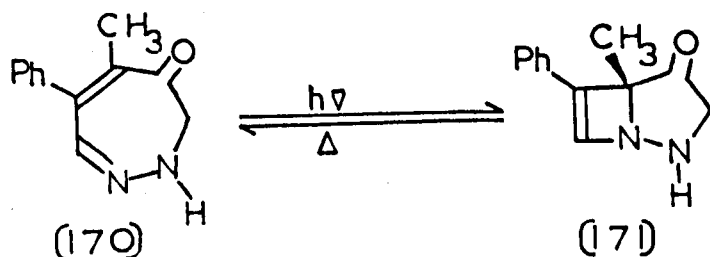
If K is the total number of  $\pi$  electrons involved and n is an integer then when  $K = 4n$  the thermal process is conrotatory and the photochemical process disrotatory. When  $K = 4n+2$  the thermal process is disrotatory and the photochemical conrotatory.

Electrocyclic reactions of systems containing the hetero atom nitrogen are not as well documented as their isoelectronic hydrocarbon counterparts. The electrocyclic cleavage of the cyclopropyl anion has not been studied directly in the parent system. The isoelectronic aziridine system has been studied as summarized in the diagram shown below.

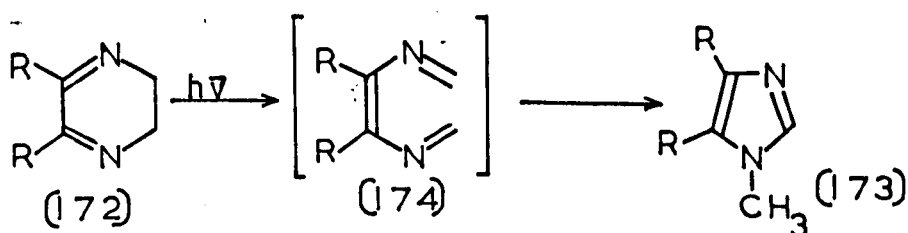


The 1,3-dipolar isomer of aziridine is a four  $\pi$  electron system which is isoelectronic with the allyl anion. The overall inversion of the stereochemistry, which is observed in the thermal process is difficult to understand unless it is realised that a conrotatory ring opening process occurs followed by a  $[4 + 2]$  cycloaddition.

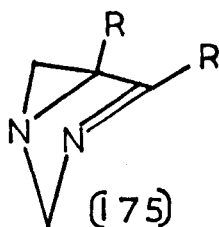
The diazepinone (170) yields on photolysis the bicyclic isomer (171) which reverts readily to the starting material on heating. A reversible reaction of this type would be impossible in the fused carbocyclic system because a direct cis-trans isomerisation is not possible. In this case the cis-trans interconversion is easy because it only involves inversion of the nitrogen atom at the bridgehead.



It has been reported<sup>71</sup> that 2,3-dialkyl-2,3-dihydropyrazines (172) undergo ready photoisomerisation to substituted imidazoles (173). It was postulated that these reactions went via the intermediate enediimine (174).

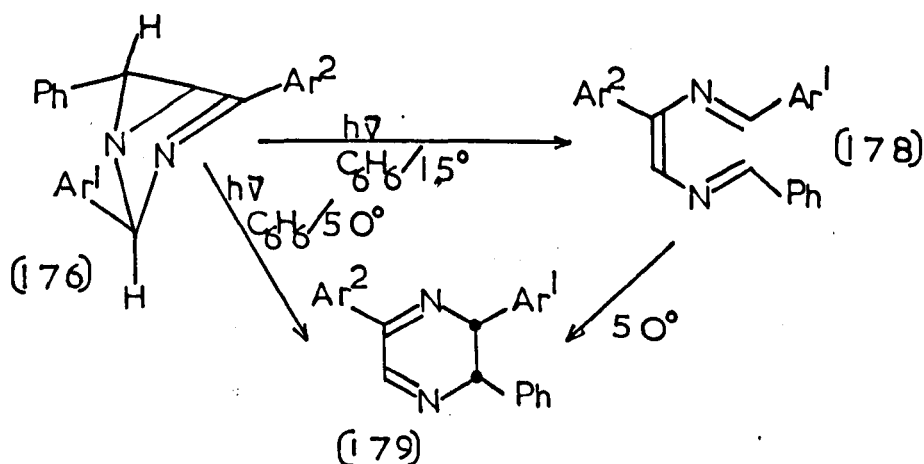


The study of 1,3-diazabicyclo [3.1.0] hex-3-ene (175) was made<sup>72</sup> because it would fulfill all the functions of the intermediate (174) in the above reactions, and as 1,3-cyclohexadienes give bicyclo [3.1.0] hex-2-enes on photolysis.

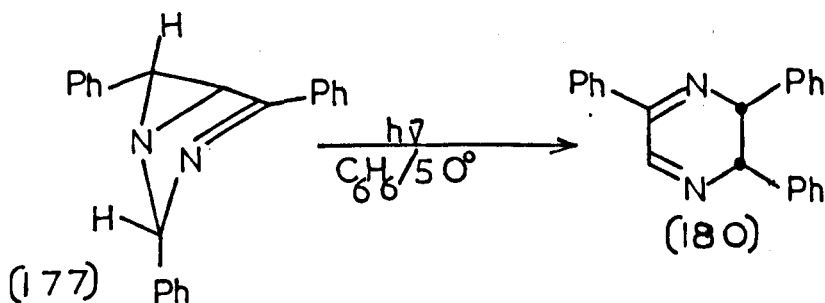


Endo and exo-2,4,6-triphenyl-1,3-diazabicyclo [3.1.0] hex-3-ene (176 and 177) have been prepared<sup>72</sup> by treating trans-2-phenyl-3-benzoylaziridine with benzaldehyde in

ethanol with ammonia and a trace of ammonium bromide. The photochemical ring opening of the bicyclic system (176) to the trans, cis, trans enediimine (178) occurs and thermal ring closure yields only the cis dihydropyrazine (179). This would be predicted by orbital symmetry considerations. However, although orbital control is implicated it has been shown that ring opening occurs in a stepwise manner via the formation of a 1,3-dipolar intermediate.

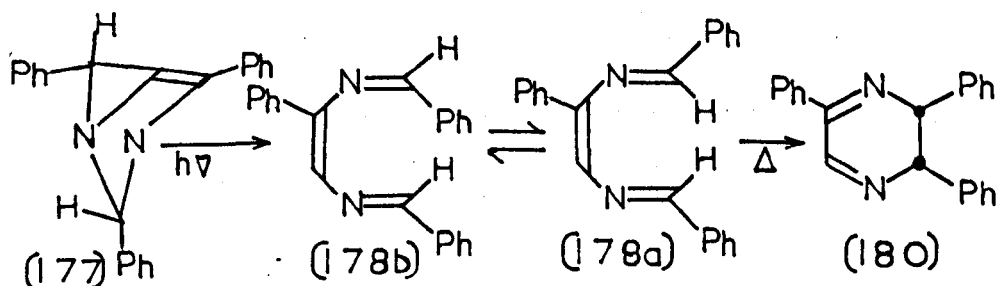


Irradiation of compound (177) was expected to give trans-2,3-dihydropyrazine but irradiation at 50°C gave only cis-dihydropyrazine (180).

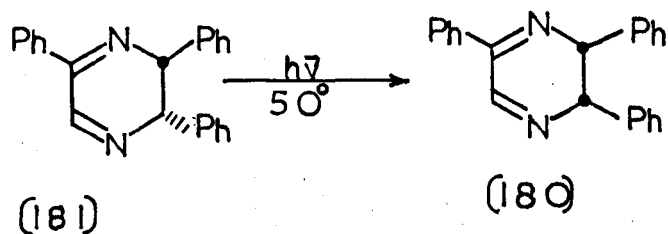


These results were explained by assuming that the enediimine existed as an equilibrium mixture of (178a) and

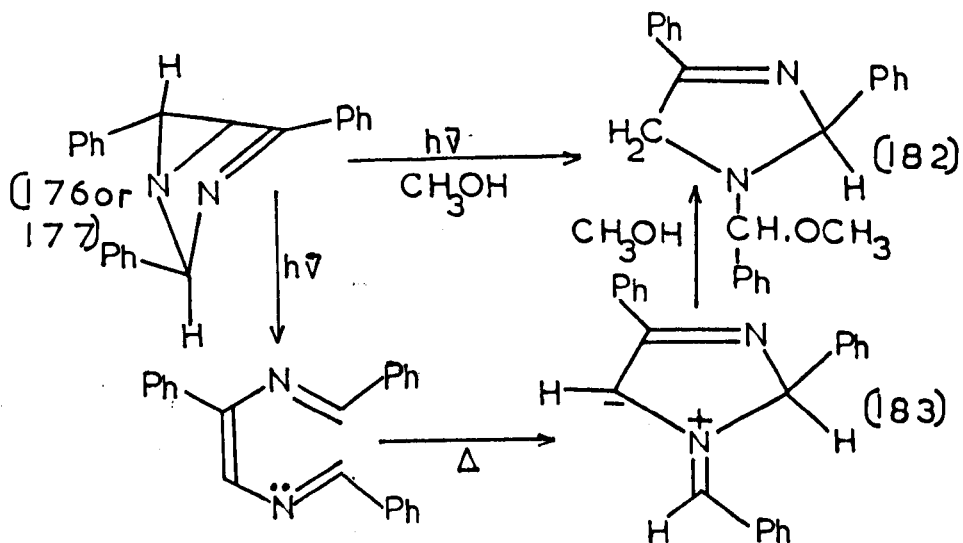
(178b) the more prevalent isomer being (178a). The first step of the ring opening of compound (177) was to the enediimine (178b), followed by rapid isomerisation to the enediimine (178a) which underwent thermal disrotatory ring closure to the dihydropyrazine (180).



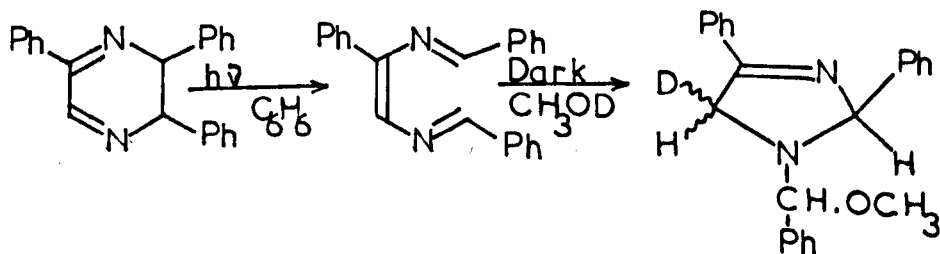
This was supported by the observation that the trans dihydropyrazine (181) was converted to the cis isomer on photolysis at 50°C.



On irradiation of either isomer (176 or 177) in methanol a high yield of 2,4-diphenyl-1-methoxybenzilimidazoline (182) was produced. This was explained by the involvement of the ylide intermediate (183) which could arise from the enediimine, as shown, or directly from the aziridine by cleavage of the C-C bond.



Production of the ylide (183) was supported by an experiment in which the photolysis was carried out in monodeutero methanol. The deuterium then appeared at position 5 (50% trans, 50% cis).



It was assumed that the polar solvent was able to solvate the developing charges of the ylide which was why a different pathway occurred on changing the solvents from benzene to methanol.

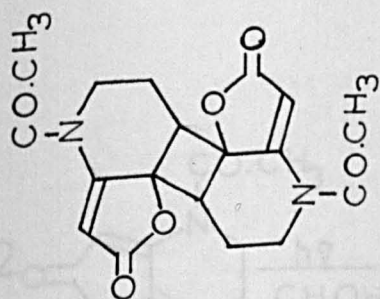
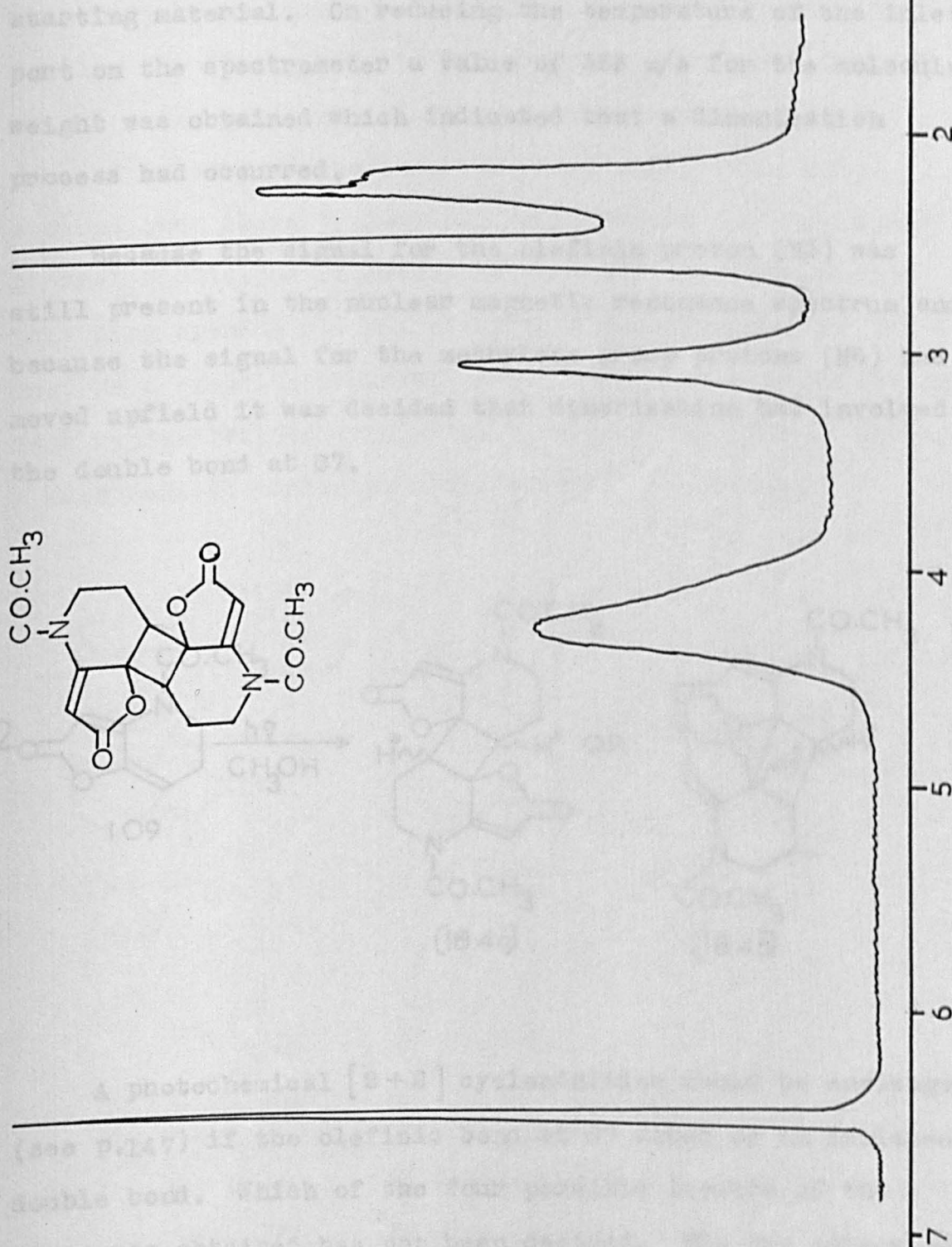
### Discussion.

During the attempts to establish the structure of the furopyridone (109) a photolysis experiment was carried out. The furopyridone (109) was dissolved in methanol and photolysed using a pyrex filter in the hope of obtaining a simple pyridine derivative whose structure could be assigned and from which the structure of the starting material might be deduced. The experiment was followed by thin layer chromatography and after three hours the conversion appeared to be complete, the  $R_f$  values changing from 0.4 to 0.1.

The product was rather insoluble recrystallising from large volumes of methanol and having a high melting point ( $\sim 200^\circ\text{C}$ ). The infrared spectrum which was run as a mull due to the insolubility of the material showed the presence of two carbonyl groups ( $1765, 1685\text{ cm}^{-1}$ ). These values were similar to those obtained for the dihydrofuropyridone (124) ( $1740, 1687\text{ cm}^{-1}$ ). The nuclear magnetic resonance spectrum (p.157) run in trifluoroacetic acid showed the presence of the N-acetyl methyl group as a singlet absorption at  $\delta 2.6$  p.p.m. A comparison of this spectrum with that of the starting material (109) also run in trifluoroacetic acid showed that two of the signals had altered. The split triplet originally at  $\delta 6.25$  p.p.m. had disappeared and a broad singlet absorption at  $\delta 3.12$  p.p.m. had taken its place. The signal due to methylene protons at  $\delta 2.8$  p.p.m. had moved upfield to  $\delta 2.3$  p.p.m. which indicated that the deshielding



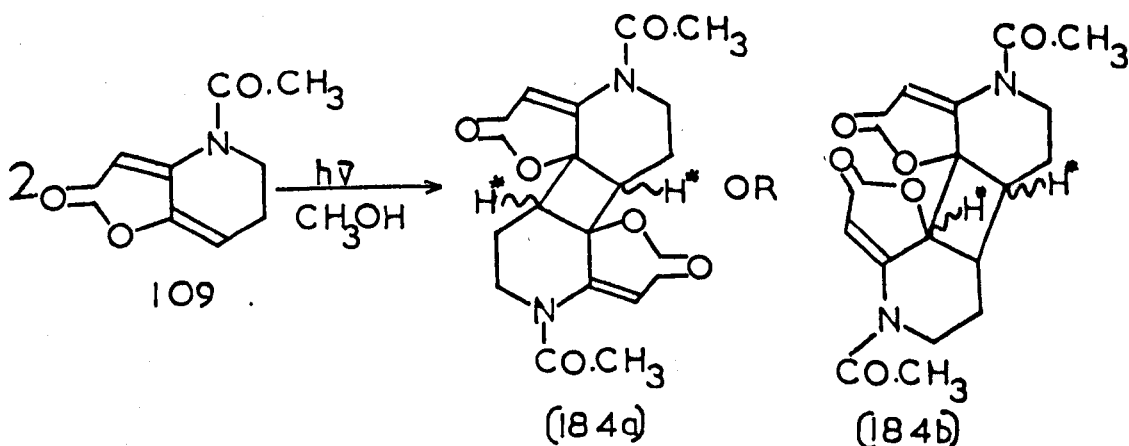
N.M.R. Spectrum Of The  
Dimer of the furopyridone (109).



effect of the adjacent double bond had been removed.

The initial mass spectrum of the material gave a picture which was superimposable on that obtained for the starting material. On reducing the temperature of the inlet port on the spectrometer a value of 358 m/e for the molecular weight was obtained which indicated that a dimerisation process had occurred.

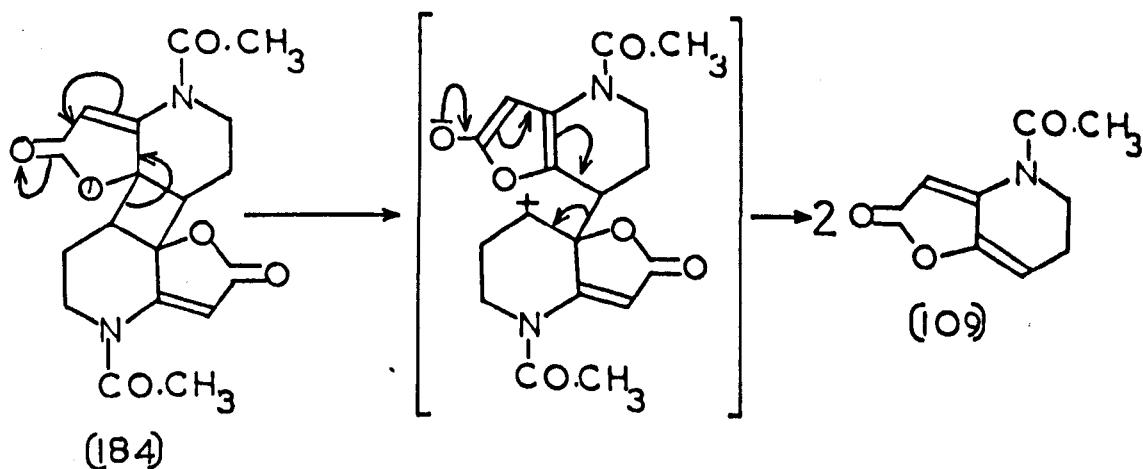
Because the signal for the olefinic proton (H3) was still present in the nuclear magnetic resonance spectrum and because the signal for the methylene group protons (H6) had moved upfield it was decided that dimerisation had involved the double bond at C7.



A photochemical [2+2] cycloaddition could be envisaged (see p.147) if the olefinic bond at C7 acted as an isolated double bond. Which of the four possible isomers of the dimer was obtained has not been decided. The two molecules

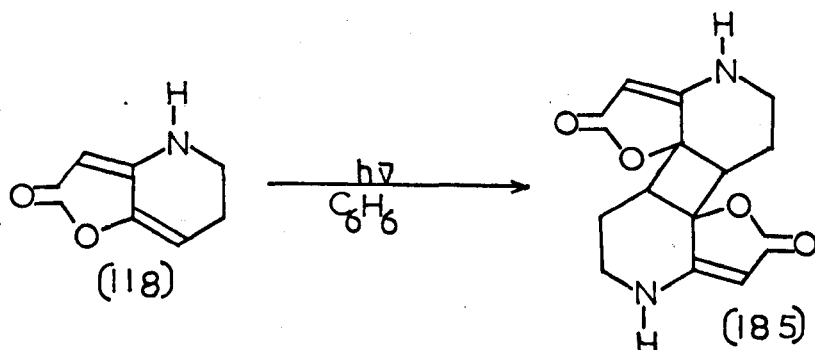
could add together head to tail (184a) or head to head (184b) and the protons marked could be cis or trans to each other.

The indication that the reaction was reversible which was shown by the mass spectrum proved to be correct. On heating the dimer (184) to its melting point under reduced pressure the monomeric starting material sublimed in the form of colourless needles. The Woodward-Hofmann rules suggest that these cyclobutane rings should not open under thermal conditions (p.148). It is therefore assumed that this ring opening did not occur in a concerted manner but must be a stepwise process. A possible mechanism involving bond reorganisation within the five membered ring is shown, a free radical mechanism could also be postulated.

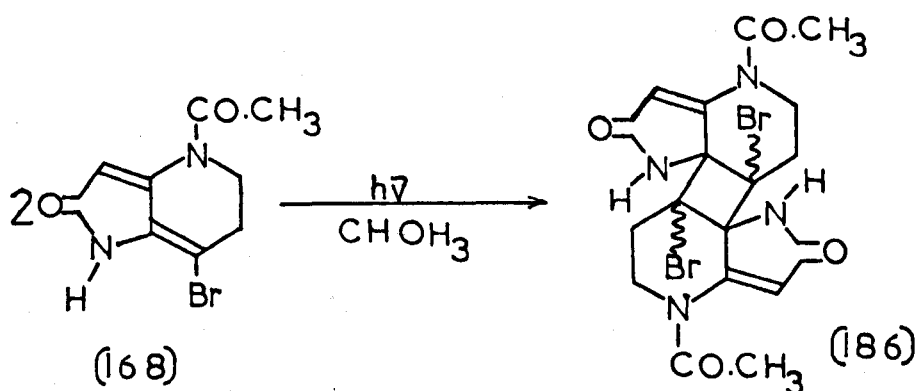


The dimer (184) hydrolysed readily when an ethanolic solution was treated with sodium hydroxide solution to give a product (185) identical with that obtained from the

photolysis of the furopyridone (118) in benzene (p.166).



A very dilute methanolic solution of the pyrrolopyridone (168) was photolysed in order to study the effects of the halogen atom on the dimerisation process. It was hoped that the halogen atom would effectively stop the [2+2] cycloaddition process and so cause the pyridine ring to open in a manner similar to that seen for the furopyridone (118) (p.161). The dimerisation process still occurred but the yield of the dimer produced was reduced to 44%.



It was not decided which isomer was obtained out of the four possibilities.

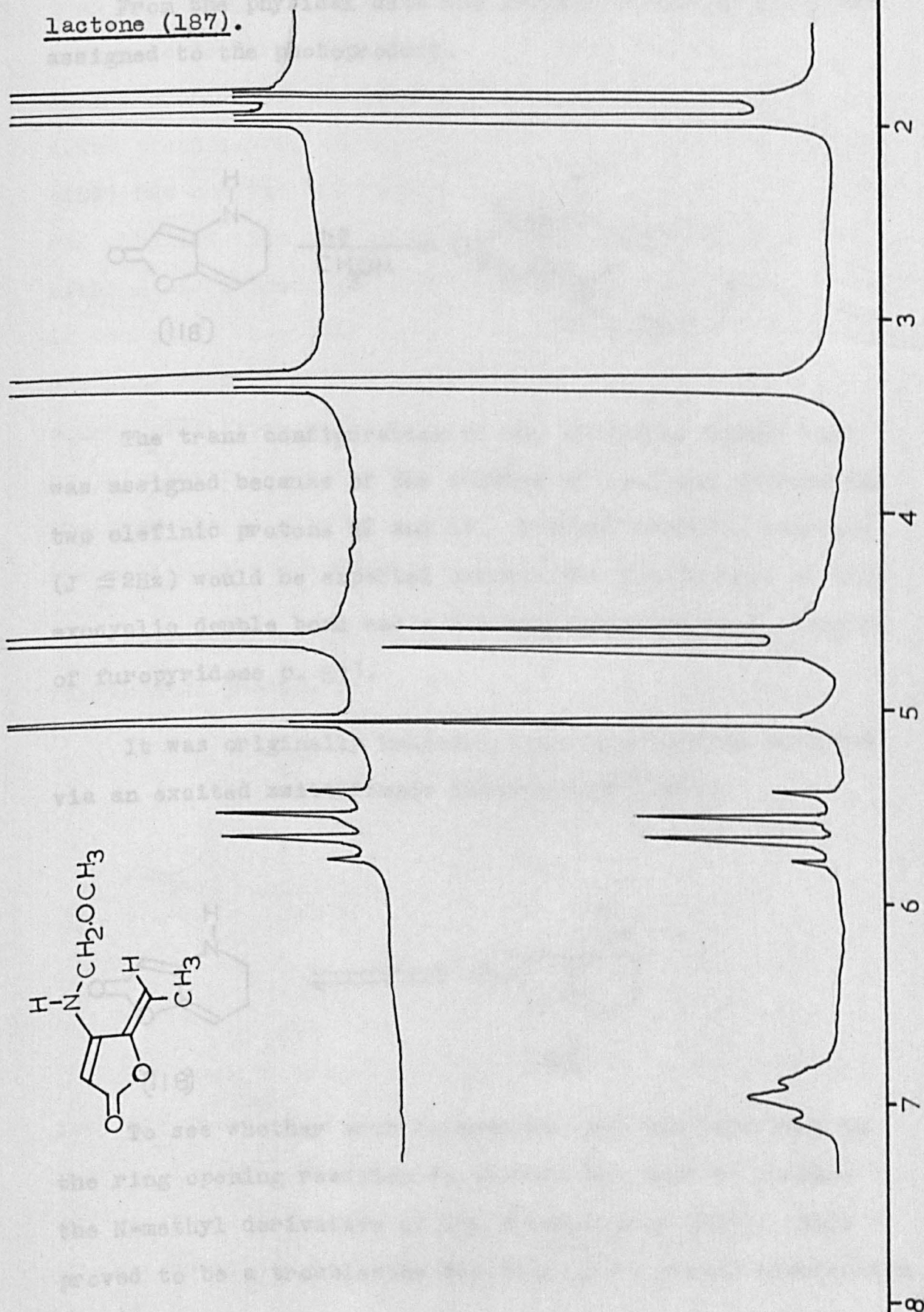
The furopyridone (118) was photolysed in methanol in

an attempt to prepare the dimer (185). This reaction was followed by thin layer chromatography and after four hours the reaction was terminated since it was obvious by the number of components produced and their  $R_f$  values, that the dimer was not being produced. The crude product was eluted up preparative layer chromatography plates using a mixture of chloroform, methanol and ethyl acetate (70:10:20) as the eluent. Only one product was isolated ( $R_f$  0.4), this was recrystallised from benzene to give a white crystalline solid m.p. 134-136°C. The mass spectral and analytical data gave the molecular formula as  $C_8H_{11}NO_3$ . The infrared spectrum had three major bands, 3440, 1750 and 1610  $cm^{-1}$  indicating the presence of an amino group, a carbonyl group (probably in a small ring) and a double bond.

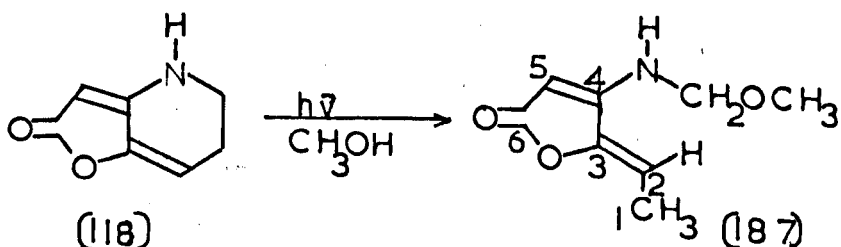
The nuclear magnetic resonance spectrum (p.162) has two methyl group signals, one as a doublet ( $J = 7Hz$ ) at  $\delta$  1.9 p.p.m. and the other as a singlet at  $\delta$  3.32 p.p.m. having the correct chemical shift for a methoxyl group. A sharp two-proton doublet occurs at  $\delta$  4.65 ( $J = 6Hz$ ) which on the addition of  $D_2O$  is transformed into a singlet. This indicates that these methylene group protons are coupled to the amino group hydrogen atom which appears as a broad exchangeable triplet at  $\delta$  7.0 p.p.m. There is also a sharp olefinic proton singlet absorption at  $\delta$  5.05 p.p.m. and a quartet at  $\delta$  5.6 p.p.m. ( $J = 7Hz$ ) due to  $H_2$  which from the coupling constant and pattern appears to be coupled to the methyl group at  $\delta$  1.9 p.p.m.

N.M.R. Spectrum Of

4-Hydroxy-3-methoxymethylamino-hexa-2,4-dienoic acid  
lactone (187).

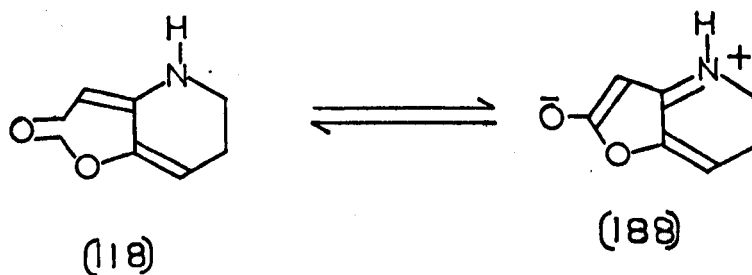


From the physical data the lactone structure (187) was assigned to the photoproduct.



The trans configuration of the exocyclic double bond was assigned because of the absence of coupling between the two olefinic protons H2 and H5. A small coupling constant ( $J \leq 2\text{Hz}$ ) would be expected between the two protons if this exocyclic double bond had a cis configuration (c.f. spectra of furopyridone p. 57).

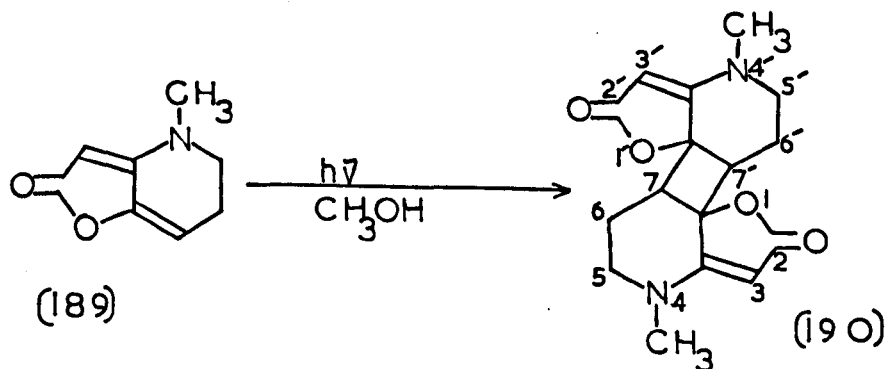
It was originally believed that ring opening occurred via an excited zwitterionic intermediate (188).



To see whether such an intermediate was important in the ring opening reaction an attempt was made to prepare the N-methyl derivative of the furopyridone (118). This proved to be a troublesome reaction since proton abstraction

from the furopyridone (118) by strong bases ( $\text{K}^+ \text{tBuO}^-$ ,  $\text{NaOEt}$ ) gave rise to large amounts of polymeric material. Use of sodium hydride as the base and methyl iodide as the methylating agent led to the isolation of the N-methyl derivative (189) but only in 45% yield. A very much better yield (73%) was obtained when the furopyridone (118) was treated with lithium bis(trimethylsilazyl) amide, and heated under reflux in benzene. When thin layer chromatography indicated complete salt formation an excess of dimethyl sulphate was added. The appearance of the methylated product was followed by thin layer chromatography, the product was isolated by treating the solution with the minimum volume of water and extraction with chloroform.

Photolysis of this N-methyl derivative (189) gave no ring-opened product but a 38% of the dimer (190) was isolated.



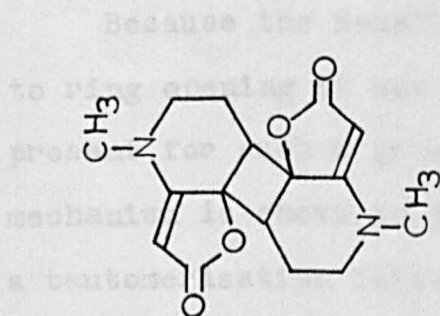
The nuclear magnetic resonance spectrum (p.165) shows that the molecule has symmetry because the  $\text{H}_3$  and  $\text{H}_{3'}$  protons and the two N-methyl group protons appear as singlets at  $\delta$  4.42 and 3.0 p.p.m. The methylene group protons  $\text{H}_6$  and  $\text{H}_{6'}$  appear as a multiplet at  $\delta$  1.8 p.p.m. and the two  $\text{H}_7$



N.M.R. Spectrum Of The

Dimer Of The Europyridone (189).

protons give rise to the  
and the two H's at the  
δ 3.70-4.04 p.p.m.



Photolysis of the Dimer

yielded no conversion of the

From this it was concluded

was probably separated

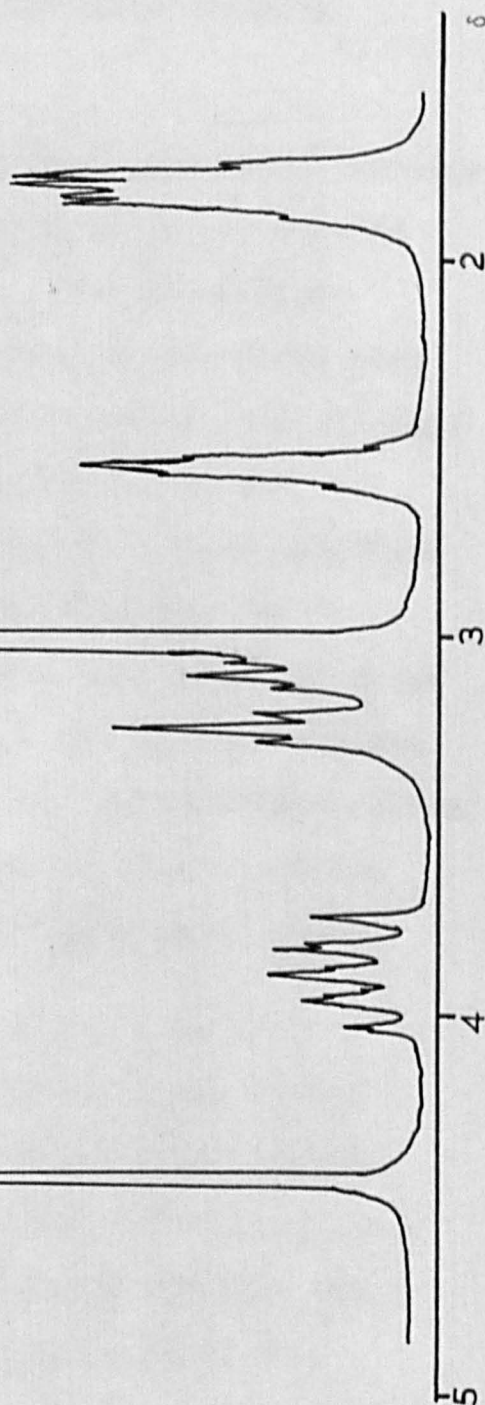
while present to react

slowly dimerization

On photolysis of the

the presence of two

dimer (189) remains



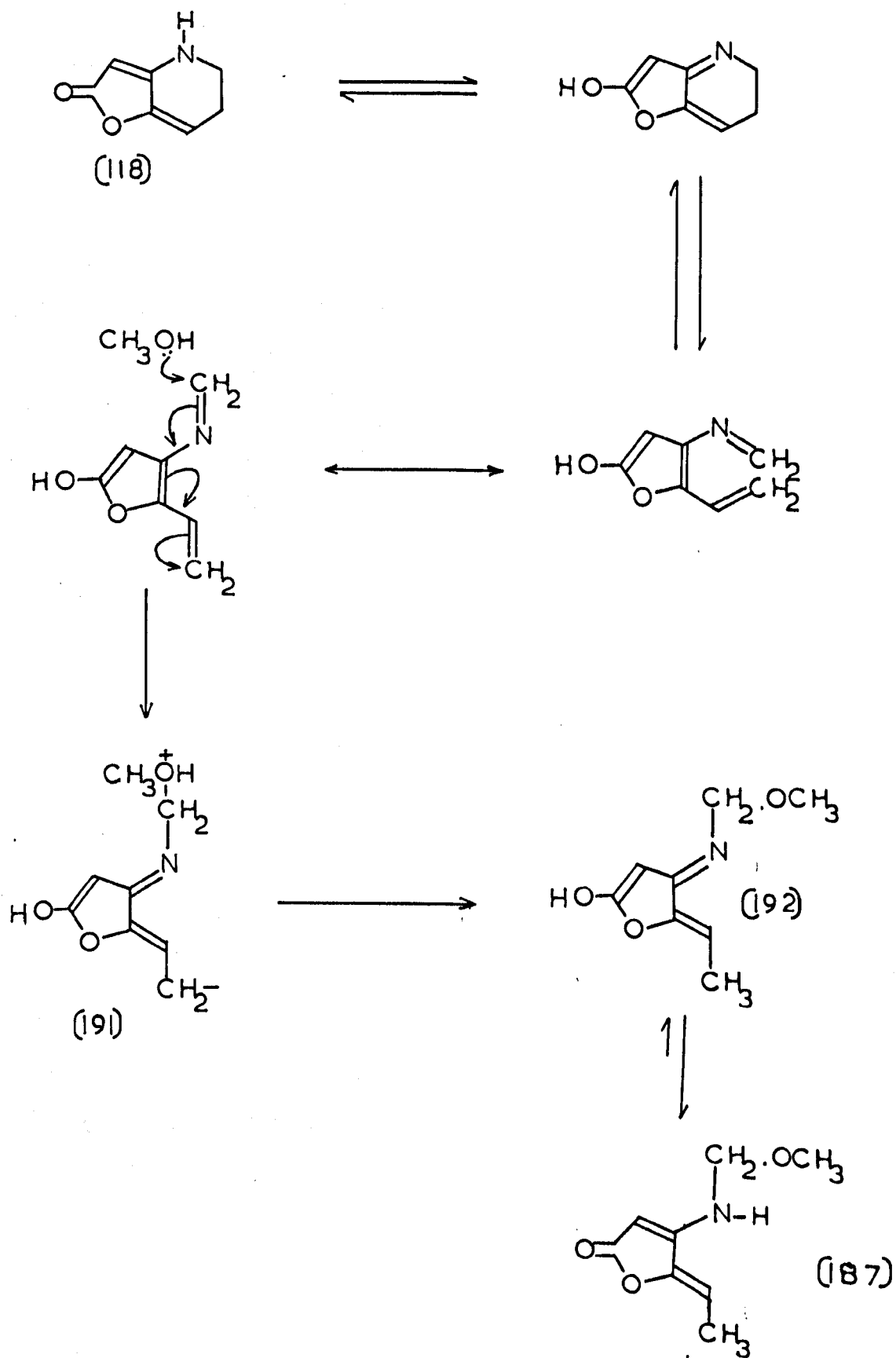
protons as a triplet at  $\delta$  2.55 p.p.m. The two H5 equatorial protons give rise to the two triplets at  $\delta$  3.1 and 3.24 p.p.m. and the two H5 axial protons to the multiplet between  $\delta$  3.70-4.04 p.p.m.

Because the N-methyl derivative (189) showed no tendency to ring opening it was decided that the proton H4 must be present for such a process to occur. The postulated mechanism is shown on p.167 and involves as the first step a tautomerisation followed by an electrocyclic ring opening. This is postulated because of its similarity to the cyclohexadiene and to the dihydropyrazine systems (p.149 and 152). At this stage it was postulated that the two exocyclic double bonds rotate away from each other in order to alleviate the steric overcrowding. Nucleophilic attack of the methanol solvent on the imine and bond reorganisation yields the zwitterion intermediate (191) which by proton transfer yields the tautomer (192) of the product (187).

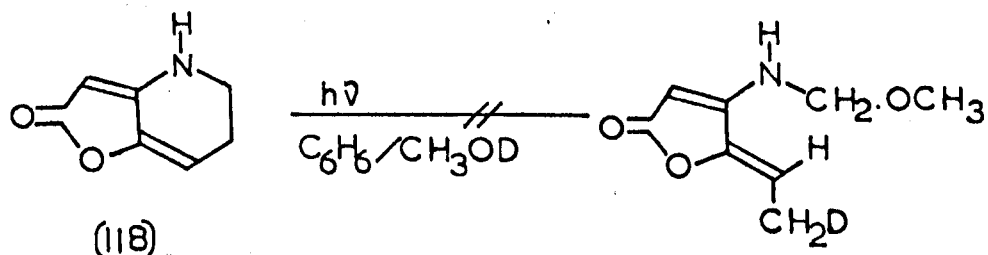
Photolysis of the furopyridone (118) in benzene yielded no monocyclic product but only the dimer (185). From this it was concluded that the ring opening process was probably reversible and that if there were no nucleophile present to react with the triene intermediate the slower dimerisation reaction became the dominant one.

On photolysing the furopyridone (118) in benzene in the presence of two moles of methanol O-D again only the dimer (185) was isolated. It had been hoped that the ring

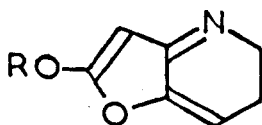
Scheme 28



opening reaction would proceed and that the deuterium atom would appear at position 1 of the product.



The possibility that the diene form of the furopyridone (118) was only produced under photolytic conditions was considered since attempts to alkylate on the oxygen with triethyloxonium fluoroborate and methyl fluorosulphonate were unsuccessful. It had been hoped that O-alkylation might force the molecule to take up the dihydropyridine form (193) whose photochemical ring opening could then be studied.

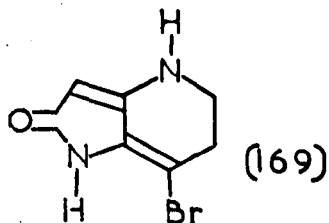


(193)

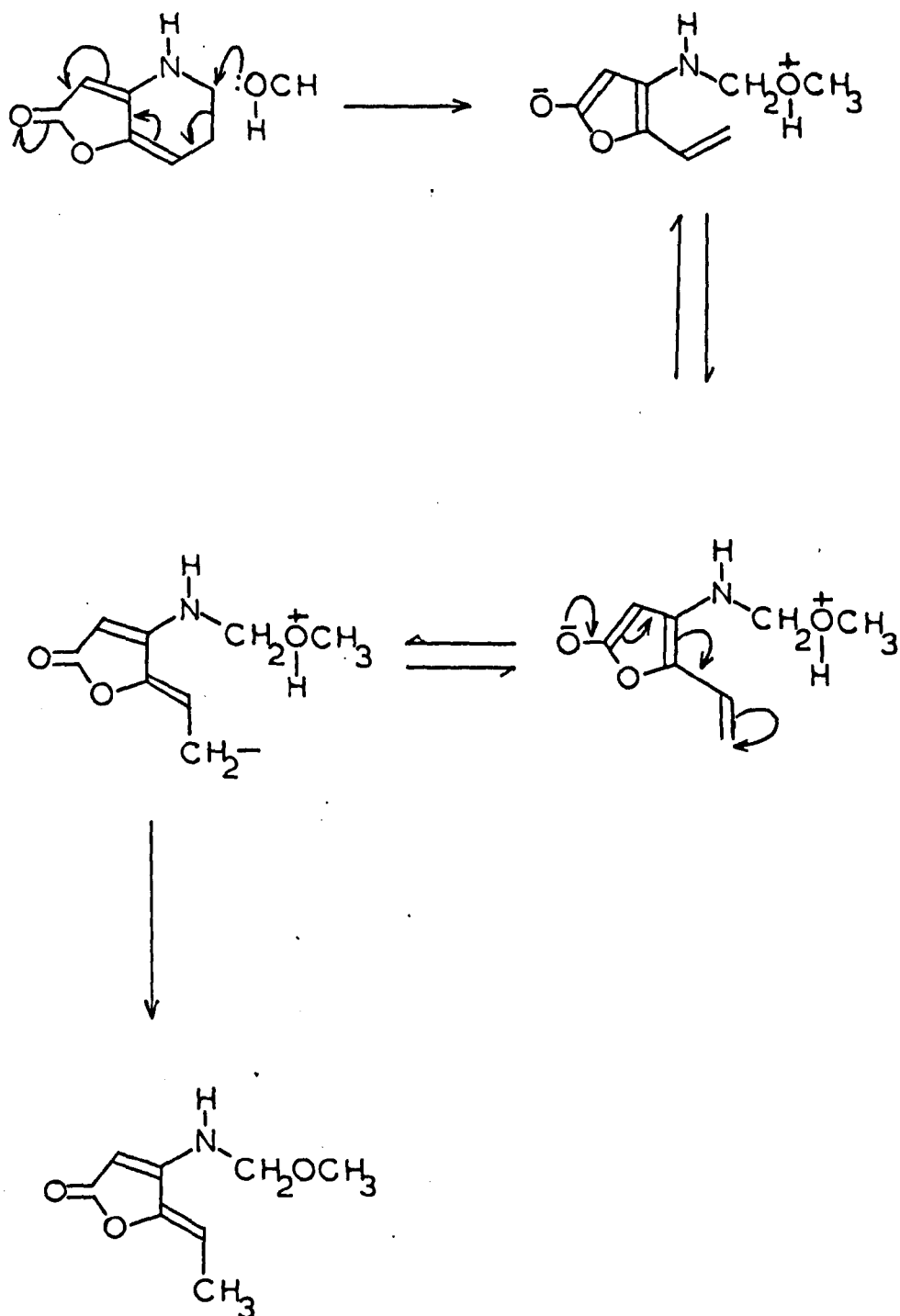
Photolysis of the furopyridone (118) in benzene in the presence of an excess of dimethyl acetylenedicarboxylate also proved unsuccessful in trapping the diene system (193,  $R = H$ ). This may have been because such a diene requires an electron rich dienophile or that the diene was not produced at all. If the latter were the case some

other ring opening mechanism must be postulated. A free radical mechanism or one involving attack of methanol as shown (p.170) are not very satisfactory because they indicate that the H4 proton is not involved. If this were the case there appears no reason why the N-methyl derivative (189) or the N-acetyl derivative (109) should not undergo the ring opening reaction.

Photolysis of the pyrrolopyridone (169) has so far only given polymeric materials and quantities of products not large enough to isolate. This pyrrolopyridone (169) appears to be rather unstable, turning orange-red on standing at room temperature for short periods. Attempts to alkylate the five membered ring nitrogen atom in order to try and increase its stability have so far failed.



Scheme 29



Experimental.

Dimer (184) of 4-Acetyl-5,6-dihydro-4H-furo [3,2-b] pyrid-2-one (109).

The pyridone (109)(0.5g) was dissolved in dry methanol (35 c.c.) and irradiated through a pyrex filter (3h.). The experiment was followed by thin layer chromatography using chloroform as the eluent.

The product crystallised out on the sides of the reaction vessel, filtration and recrystallisation from methanol gave the dimer (184) m.p. 200-201°C (0.376g, 75%).

Found	C,60.3; H,5.31; N,7.82%
$C_{18}H_{18}N_2O_6$ requires	C,60.4; H,5.05; N,7.80%
IR. (Mull)	3120, 1765, 1685, 1618 $cm^{-1}$
U.V. (95% EtOH)	276 nm (4.37)
N.M.R. (T.F.A.)	2.3(4H,m); 2.6(6H,s); 3.12(2H,m); 4.35(4H,m);6.5(2H,s) p.p.m.
Mass Spectrum (m/e)	358 ( $M^+$ )

Thermal properties of dimer (184).

The dimer (184)(0.1g) was heated to 250°C under vacuum (0.1 mm Hg) and the monomer (109)(0.095g, 95%) sublimed out. It was shown to be the monomer by mixed melting point with the pyridone (109) and by mass spectrometry.

Hydrolysis of the dimer (184).

The dimer (184)(0.51g) was dissolved in ethanol (95%, 100 c.c.) and sodium hydroxide solution (2N) added

slowly. When the hydrolysis was complete, shown by thin layer chromatography, the solution was neutralised with hydrochloric acid (2N) and the solvent evaporated. The resultant mixture was extracted with chloroform, the solvent evaporated and the hydrolysis product (185) recrystallised from methanol, this had m.p. > 300°C (0.38g, 40%)

Found	C, 60.90; H, 5.65; N, 9.9%
$C_{14}H_{14}N_2O_4$ requires	C, 61.30; H, 5.15; N, 10.22%
IR. (Mull)	3320, 3120, 1740, 1620 $cm^{-1}$
U.V. (95% EtOH)	276 nm (4.45)
N.M.R. (T.F.A.)	2.1(4H, m); 3.0(2H, br. s); 3.85(4H, m), 5.0(2H, m) p.p.m.
Mass Spectrum (m/e)	274 ( $M^+$ )

Dimer (186) of the pyrrolopyridone (168).

The pyrrolopyridone (168) (0.5g) was photolysed as described for the preparation of the dimer (184) to give the product (186) which had m.p. > 300°C (0.22g, 44%)

IR. (Mull)	3150, 1720, 1690, 1640 $cm^{-1}$
U.V. (95% EtOH)	242 nm (SHOULDER) (4.09)
N.M.R. (T.F.A.)	2.31(3H, s); 3.0(2H, m); 3.9(2H, m); 5.5(1H, s) p.p.m.
Mass Spectrum (m/e)	511.9699 ( $M^+$ )
$C_{18}H_{18}N_4O_4Br_2$ requires	511.9695 ( $M^+$ )

4-Hydroxy-3-methoxymethylamino-hexa-2,4-dienoic acid lactone (187).

The furopyridone (118) (0.5g) was dissolved in dry



methanol (35 c.c.) and irradiated (4h.). The product obtained after evaporation of the solvent was passed down an alumina column (IV, 30g) using a mixture of benzene and chloroform (50/50) as the eluent. The crude product obtained was eluted up preparative layer chromatography plates using a mixture of chloroform, methanol and ethyl acetate (70:10:30). The band ( $R_f$  0.4) was extracted with methanol, evaporated, reextracted with chloroform and filtered. The lactone (187) was obtained on evaporation of the chloroform and had m.p. 134-6°C (0.25g, 40%)(benzene).

Found .	C,57.00; H,6.50; N,8.40%
$C_8H_{11}NO_3$ requires	C,56.79; H,6.56; N,8.28%
IR ( $CHCl_3$ )	3440, 1750, 1610 $cm^{-1}$
U.V. (95% EtOH)	256.5, 296.5 nm (4.17, 3.93)
N.M.R. ( $CDCl_3$ )	1.9(3H,d J = 7Hz); 3.32(3H,s); 4.65(2H,d J = 6Hz); 5.05(1H,s); 5.6(1H,q J = 7Hz) p.p.m.
Mass Spectrum (m/e)	169 ( $M^+$ )

4-Methyl-5,6-dihydro-4H-furo [ 3,2-b ] pyrid-2-one (189).

The pyridone (118)(0.5g) was dissolved in dry benzene (30 c.c.) and to this solution lithium bis(trimethylsilazyl) amide (0.5g) was added. The solution was boiled until thin layer chromatography indicated complete salt formation. Dimethyl sulphate (excess) was added and the solution heated ( $\frac{1}{2}$ h.). Addition of water (10 c.c.) to the cooled solution, thorough extraction with chloroform and evaporation of the dried organic layer gave the N-methyl derivative (189)

which was recrystallised from benzene and had m.p. 42-45°C (0.4g, 73%).

Found	C,63.20; H,6.33; N,9.10%
$C_8H_9NO_2$ requires	C,63.56; H,6.03; N,9.27%
IR. ( $CHCl_3$ )	1758, 1620 $cm^{-1}$
U.V. (95% EtOH)	261, 316 nm (4.11, 3.92)
N.M.R. ( $CDCl_3$ )	2.75-2.30(2H,m); 2.9(3H,s); 3.25(2H,t); 4.62(1h,d J = 1Hz); 5.6(1H,t J = 4,1Hz) p.p.m.
Mass Spectrum (m/e)	151 ( $M^+$ ).

Dimer (190) of the pyridone (189).

The photolysis and work-up was carried out as described for the preparation of compound (184) and gave the dimer (190) (35%) which had m.p. 216°C(d).

Found	C,63.40; H,6.03; N,9.10%
$C_{16}H_{18}N_2O_4$ requires	C,63.56; H,6.03; N,9.27%
IR. ( $CHCl_3$ )	1730, 1630 $cm^{-1}$
U.V. (95% EtOH)	237, 277 nm (3.99, 4.46)
N.M.R. ( $CDCl_3$ )	1.80(4H,m); 2.55(2H,m); 3.0(6H,s); 3.10(2H,t); 3.24(2H,t); 3.70-4.04(2H,m); 4.42(2H,s) p.p.m.
Mass Spectrum (m/e)	302 ( $M^+$ ).

Dimer (185) of the furopyridone (118).

Photolysis of the furopyridone (118)(0.5g) in benzene (40 c.c.)(4h.) and evaporation of the solvent gave the dimer (185)(0.1g, 20%) identical with that obtained by the

hydrolysis of dimer (184).

Photolysis of the pyridone (118) in the presence of  $\text{CH}_3\text{OD}$ .

The experiment was carried out as described above except that two molar equivalents of methanol (O-D) were added to the benzene solution only the dimer (185)(18%) was isolated.

Attempted O-alkylation of the furopyridone (118).

A boiling benzene solution of the pyridone (118)(0.5g) was treated with Meerweins' reagent (0.6g) and heated overnight. On adding aqueous sodium bicarbonate solution a yellow gum was obtained. This gum was insoluble in water and in most organic solvents.

A similar gum was produced when the pyridone (118) was dissolved in dichloromethane, methyl fluorosulphonate added and after boiling (16h.) the solution washed with aqueous sodium bicarbonate solution.

These gums had very ill defined nuclear magnetic resonance spectra and would not give a mass spectrum.

The reaction of dimethyl acetylene dicarboxylate with the pyridone (118).

The pyridone (118)(0.2g) was dissolved in dry benzene, dimethyl acetylene dicarboxylate (2g) added and the solution photolysed. After five hours the only materials isolated

were the furopyridone (118) and its dimer (185).

Photolysis of the pyrrolopyridone (169).

The pyridone (169)(0.4g) was dissolved in methanol (35 c.c.) and the solution irradiated (4h.). Thin layer chromatograms (chloroform/10% methanol eluent) indicated the presence of many components. An attempt to separate these components by preparative layer chromatography showed that the majority of the material remained at the origin.

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